

**Somatic morbidity among dependent opioid users before, during and after
opioid maintenance treatment**

Longitudinal cohort studies of acute and subacute disease incidents

Dissertation (PhD)

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2012

SERAF

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UNDER BERGFALLET

*Du bur under bergfall.
Og du veit det.
Men sår din åker
og trør trygt ditt tun
og lèt dine born leika
og legg deg
som inkje var.*

*Det hender,
når du stør deg til ljåen
ein sumarkveld,
at augo sviv som snarast
yver bergsida
der dei segjer
sprekken
skal vera,
og det hender
du vert liggjande vaken
og lyda etter
steinsprang
ei natt.*

*Og kjem raset,
kjem det ikkje uventa.
Men du tek til å rydja
den grøne boti
under berget
- um du då har livet.*

*Olav H. Hauge
1951*

*Taken from
Dikt i samling
Det Norske Samlaget
2004*

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Ivar Skeie

Oslo/Gjøvik September 2012

Abbreviations

AIDS	Acquired immune deficiency syndrome
ATOS	Australian Treatment Outcome Study
CI	confidence interval
CMR	crude mortality rate
CNS	central nervous system
ER	Even Reinertsen
GAS	group A streptococcus
GP	general practitioner (physician)
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IDU	injecting drug user
IR	incidence rate
IRR	incidence rate ratio
IS	Ivar Skeie
6-MAM	6-monoacetylmorphine
MRSA	meticillin resistant staphylococcus aureus
OMT	opioid maintenance treatment
PCR	polymerase chain reaction
RCT	randomised controlled study
SMR	standardized mortality ratio
SPSS	Statistical Package for the Social Sciences
UK	United Kingdom
US	United States of America
WHO	World Health Organization

List of papers

I

Skeie I., Brekke M., Lindbæk M. & Waal H. (2008) Somatic health among heroin addicts before and during opioid maintenance treatment: a retrospective cohort study. BMC Public Health. 2008 Jan 31;8:43, doi:10.1186/1471-2458-8-43

II

Skeie I., Brekke M., Gossop M., Lindbaek M., Reinertsen E., Thoresen M. & Waal H. (2011) Changes in somatic disease incidents during opioid maintenance treatment: results from a Norwegian cohort study. BMJ Open. 2011 Jan 1;1(1):e000130. Epub 2011 Aug 6, doi:10.1136/bmjopen-2011-000130

III

Skeie I., Brekke M., Clausen, T., Gossop M., Lindbaek M., Reinertsen E., Thoresen M. & Waal H. (2012) Increased somatic morbidity in the first year after leaving opioid maintenance treatment: results from a Norwegian cohort study. Submitted.

Summary

Dependent opioid users, especially those who inject heroin, suffer far increased morbidity and mortality compared to the general population. Maintenance treatment with long-acting opioids, in Norway called medication assisted rehabilitation, is the most widely used treatment for opioid dependence in Norway and worldwide. Studies from several countries have shown reduced mortality during opioid maintenance treatment (OMT). Systematic studies on the impact of OMT on somatic morbidity have, however, been scarce.

In this thesis findings from two cohort studies investigating the size of acute and subacute somatic morbidity among dependent opioid users – prior to, during and after interruption of OMT – are presented. Disease incidents were divided into three main categories: drug-related, non-drug-related and injuries and drug-related incidents were divided into the sub-categories overdose, injecting-related and “other”. In Study 1 (Paper 1), comprising 35 OMT patients from Gjøvik municipality, the volume of treatment in hospitals, by general practitioners (GPs) and in emergency wards while patients were receiving OMT was compared to the out-of-treatment period. In Study 2 (Paper 2 and Paper 3), comprising 200 OMT patients from the counties Hedmark and Oppland, only hospital treatment was assessed, and disease incidents before, during and after OMT were compared. How acute somatic morbidity before, during and after OMT was influenced by various patient characteristics was also examined in this study.

Both studies showed a substantial reduction in acute drug-related treatment episodes during OMT compared to the out-of-treatment period. In Study 1 a 62% reduction in total drug-related incidents leading to treatment in hospitals, emergency wards and by GPs was found, while injecting-related episodes were reduced by 70%, both findings were statistically significant. Non-drug-related episodes and injuries did not show statistically significant changes. Treatment episodes out of OMT were more often related to drug use (62%) than during OMT (36%). GPs treated a greater part of the disease incidents while patients were in maintenance treatment (40%) than out of treatment (25%). Both these findings were statistically significant.

In Study 2 the out-of-OMT period was divided in time before the first admission to OMT and time out of treatment (one or consecutive periods) after the first OMT period. We found a 76% reduction in total drug-related acute and subacute somatic disease incidents leading to hospital treatment during compared to before OMT. The reduction in injecting-related incidents was 83%, in overdoses 64% and 81% in other drug-related incidents; all these findings were statistically significant. Patients with ongoing drug-taking during OMT showed less reduction than those not using drugs, but even among these the reduction was statistically significant. Non-drug-related episodes were 35 % more frequent during OMT than before (statistically significant) while injuries were unchanged.

Paper 3 focuses on the 25 % of the patients who interrupted their OMT during the observation period. 85 % of the interrupters were unstable and taking drugs when leaving OMT, hence the great majority of the interrupters in this sample left treatment because of treatment problems. The interrupter group showed less reduction than the non-interrupters in drug-related treatment episodes during OMT compared to the pre-OMT period, but the reduction was still significant. The first year after leaving OMT the interrupters showed a substantial and statistically significant increase – both compared to the during-OMT and the prior-to-OMT periods – in drug-related disease incidents, especially the first months, and for overdoses especially the first four weeks.

Conclusion

The two studies demonstrate a considerable reduction in drug-related acute and subacute somatic disease incidents leading to health service treatment during OMT. This holds not only for patients achieving stable social rehabilitation without problem use of drugs and alcohol but even for the group with ongoing problem behaviour and drug-taking. This demonstrates the overall health-related benefit associated with OMT. Among OMT interrupters acute and subacute drug-related somatic morbidity is substantially increased after interruption of maintenance treatment, especially the first months. This should have implications for how to treat patients not reaching stable drug-free rehabilitation within OMT programs.

Sammendrag

Opioidavhengige, særlig de som injiserer heroin, har langt høyere sykkelighet og dødelighet enn befolkningen som helhet. Substitusjonsbehandling med langtidsvirkende opioider, i Norge kalt legemiddelassistert rehabilitering ved opioidavhengighet (LAR), er den mest utbredte behandlingsform for opioidavhengighet i Norge og ellers i verden. Studier fra mange land har vist at substitusjonsbehandling reduserer dødeligheten. Hvordan LAR påvirker sykkeligheten er imidlertid lite systematisk studert.

I denne avhandlingen presenteres funn fra to kohortstudier der omfanget av akutte og subakutte somatiske sykdomstilfeller hos opioidavhengige før, under og etter avsluttet LAR ble studert. Bare sykdomstilfeller som førte til behandling i helsevesenet ble inkludert og de ble delt i tre hovedgrupper, rusrelaterte og ikke-rusrelaterte tilfeller og skader. De rusrelaterte tilfellene ble delt i undergruppene overdoser, injiseringsrelaterte og "andre". I den Studie 1 (Artikkel 1), som omfattet 35 LAR-pasienter fra Gjøvik kommune, ble behandling i sykehus, hos allmennleger og ved legevakter studert og omfang av behandling mens pasientene var i LAR ble sammenlignet med tiden de ikke var i LAR. I Studie 2 (Artikkel 1 og Artikkel 2), som omfattet 200 LAR-pasienter fra Oppland og Hedmark fylker, så vi bare på sykehusbehandling, og behandling før, under og etter LAR ble sammenlignet. I denne studien så vi også på hvordan ulike egenskaper hos pasientene påvirket forekomsten av sykdomsepisoder før, under og etter LAR.

I begge studiene ble det påvist en betydelig reduksjon i akutte rusrelaterte sykdomstilfeller mens pasientene var i LAR sammenlignet med tiden de ikke mottok LAR-behandling. I Studie 1 var den samlede reduksjonen av rusrelaterte tilfeller 62% og reduksjonen i injiseringsrelaterte tilfeller var 70%. Begge disse funnene var statistisk signifikante. Tilfeller uten relasjon til rus og skader viste ikke signifikant endring. Sykdomstilfeller utenfor LAR var oftere rusrelaterte (62%) enn i LAR (36%). Allmennlegene behandlet en større andel av sykdomstilfellene når pasientene var i LAR (40%) enn når de ikke var i LAR (25%). Begge disse funnene var statistisk signifikante.

I Studie 2 ble tiden utenfor LAR delt i tid før den første behandlingsperioden i LAR og tid utenfor LAR (en eller flere perioder) etter den første LAR-perioden. Reduksjonen i antall

akutte og subakutte rusrelaterte somatiske sykdomsepisoder som medførte sykehusbehandling var 76% under LAR-behandling sammenlignet med før LAR. Reduksjonen i injiseringsrelaterte tilfeller var 83%, i overdoser 64% og i andre rusrelaterte tilfeller 81%. Alle disse funnene var statistisk signifikante. Reduksjonen blant pasienter som fortsatte å bruke rusmidler mens de var i LAR var mindre enn blant dem som var rusfrie, men reduksjonen var likevel statistisk signifikant blant den firedelen som ruset seg mest mens de var i LAR. Ikke-rusrelaterte sykdomstilfeller økte med 35 % (statistisk signifikant) mens omfanget av skader ikke endret seg.

Artikkel 3 har fokus på de 25 % av pasientene som avbrøt behandlingen i løpet av observasjonsperioden. Av disse ble bare 15 % ansett som stabile og rusfrie da de forlot LAR, resten var ustabile og brukte rusmidler. For det store flertallet som avbrøt LAR, skyldtes altså dette problemer i behandlingen. Ved sammenligning av perioden i LAR med perioden før behandling, viste avbruddsgruppen en mindre, men likevel statistisk signifikant, reduksjon i rusrelaterte tilfeller enn gruppen uten avbrudd. Det første året etter avbrudd i behandlingen opplevde avbruddsgruppen en stor økning i rusrelaterte sykdomstilfeller, særlig de første månedene, og for overdoser særlig de første fire ukene.

Konklusjon

De to studiene som danner grunnlaget for denne avhandlingen, viser at akutt og subakutt somatiske sykkelighet blir betydelig redusert mens pasientene er i LAR. Dette gjelder ikke bare for dem som oppnår stabil sosial rehabilitering og rusfrihet, men også for pasienter med vedvarende problematferd og rusmiddelbruk i LAR. Blant dem som avbryter LAR, øker den akutte rusrelaterte sykkeligheten kraftig etter avbrudd i behandlingen, særlig de første månedene. Dette bør ha betydning for hvordan pasienter som ikke oppnår stabil rusfrihet, skal behandles i LAR.

Erratum list

Page 20 line 5: psychoactive *drugs* is replaced by psychoactive *substances*

Page 21 last paragraph "Opioid effects" line 1: after *central nervous system* the abbreviation (*CNS*) is inserted

Page 21 last paragraph "Opioid effects" line 6: *dependence* is removed and in line 7 *addiction* is replaced by *dependence*

Page 23 paragraph 2, line 12: *durability* is changed to *length*

Page 24 paragraph "Mechanism of overdose" line 4: *central nervous system* is deleted, only the abbreviation *CNS* is used

Page 25 last three lines: "Overdoses due to methadone and buprenorphine show the same age profile and most such cases occur *out of maintenance treatment* indicating diversion from OMT programs 66,81,84,89-91 " is replaced by "Overdoses due to methadone and buprenorphine show the same age profile and most such cases occur *among patients not in maintenance treatment at the time of overdose* indicating diversion from OMT programs 66,81,84,89-91 "

Page 26 paragraph 3 line 2: character size of *which* is corrected

Page 31 section 2.1, line 9: *on* is replaced by *in*

Page 32 line 9: space between *pre-* and *and* is inserted

Page 42 line 4: Before *Three variables* the following is inserted *Regarding drug-related episodes (three variables...)*

Page 42, Section 4.3, paragraph 2, line7: *total* is inserted before *drug-related*

Page 43, paragraph 1: the explanation in brackets is inserted after *drug-related episodes*, the sentence should be like this: *Among the other (not overdoses or injecting-related) drug-related episodes (see Table 1, Paper 2 for definition), contacts due to "impaired general health condition" showed the greatest increase.*

Page 43, paragraph 3, line 8: *per cent* is inserted after *15*, this is essential to the meaning.

Page 44, line 13: *Overdoses* is replaced by *Non-fatal overdoses*

Page 46, line 1: *experienced* is replaced by *showed*

Page 48, paragraph 4, line 1: *are* is removed, unless the sentence is meaningless, the sentence should be: *"The OMT-related changes in health service expenditures in accordance with the changes in consumption of health care services and especially hospital treatment have not been addressed in this thesis."*

Page 48, paragraph 4, line 5: *mental and drug-related disorders* is replaced by *substance-use-related mental and behavioural disorders*

Page 52, paragraph 2, line 2: At the end of the sentence ending *before OMT, in Study 2*, is added.

Page 53, paragraph 4, line 5: The last sentence in the paragraph is modified and merged with the foregoing sentence, which is now like this:

“There were statistical significant reductions in overall number of disease incidents, in substance-related incidents and in injection-related incidents during OMT as compared to the out-of-OMT period and there was a non-significant tendency towards reduction in non-fatal overdoses.”

Page 56, paragraph 1, line 1: - is removed, the sentence is no: *“1) High participation rate among patients in as well as out of OMT when invited.”*

In the printed version of Paper 1 there is an erratum in the heading of Table 5. It says: “22 patients with and 9 patients without problematic* illicit drug use during OMT”. The correct numbers are 22 patients **without** and 9 patients **with** problematic illicit drug use. The numbers are correct in the rest of the table and in the text.

1 Introduction

1.1 Illicit opioid use – size and consequences

Although non-medical use of opium has been known for centuries and illicit use of opiates like morphine and heroin has been seen for more than a century, the “modern illicit opioid problem” mainly related to heroin use has evolved during the last fifty years to become a major societal and public health problem worldwide. The global production of heroin has more than doubled since 1985¹. United Nations World Drug Report 2010 estimated that between 13 and 22 million people globally used illicit opioids in 2008, i.e. between 0.3% and 0.5% of the world’s population aged 15 – 64. The overall heroin use and the related health problems in Western and Central Europe is assessed as stable^{2,3}. In Norway the number of problem heroin users (heroin users complying with the ICD-10 diagnostic criteria for harmful opioid use or opioid dependence⁴) was estimated to about 9 500 in 2008 including about ¼ of the patients in the national opioid maintenance treatment (OMT) programme (the rest of the OMT patients were not reckoned as present problem heroin users), and about 8 000 of these problem users were injecting⁵. In 2009 the total number of injecting drug users (IDU) in Norway was estimated to between 8 700 – 12 300⁶.

Non-medical use of prescription opioid drugs is also an increasing problem, not least in North America⁷. This alternative path into opioid dependence may be of increasing importance⁸.

Problem drug users often fail to obtain and sustain an ordinary social life and private economy. They often drop out of education, many have minimal occupational experience and are unable to stay in ordinary employment and are thus frequently dependent on social security benefits or disability pension. World Health Organization (WHO) estimated the size of Disability Adjusted Life Years (the number of years lost due to ill-health, disability or early death) attributed to illicit drug use to 6.9 millions in 2000⁹, and use of illicit drugs is ranked eighth among causes of disease, death and disability in developed regions of the world¹⁰. Problem drug use is also closely related to criminality and drug trafficking. Expenses for addiction treatment and health services related to mental and physical comorbidity are substantial. Equally important are the human costs for the individual dependent drug user, their families and close networks.

1.2 Opioid Dependence

Drug-dependence – general aspects

Drug dependence is a complex phenomenon involving elements of choice (rational/informed or irrational/ill-informed), habit, conditioning and learning¹¹. Specific changes in brain functions related to repeated and prolonged use of potentially addictive psychoactive substances seem to play a fundamental role in development of drug dependence. In addition to specific characteristics associated with single drugs or drug classes (like opioids), addictive drugs have in common the ability to activate the mesocorticolimbic system, particularly the ventral tegmental area, nucleus accumbens, amygdala and prefrontal cortex mainly via dopaminergic pathways. This system constitutes a common pathway through which addictive drugs mediate their reinforcing effects often called the “reward circuit of the brain” or the “neurocircuitry of addiction”^{12,13}.

In an evolutionary perspective the reward system can be seen as a system that has evolved to reinforce behaviours favourable for survival and reproduction^{14,15}. Endogenous opioids, like endorphins and enkephalins, activate opioid receptors of dopaminergic neurons in the mesocorticolimbic system, leading to perceived pleasure and well-being. During activities, as eating, physical exercise or reproductive activities like sex and childcare, the reward system is activated by endogenous opioids. Hence, evolutionary favourable activities are rewarded and reinforced. However, when the reward system is stimulated, not by natural activities, but by drugs acting directly on the mesocorticolimbic system and to which humans are not adapted through evolutionary and/or environmental history, this leads to supraphysiological activation creating stimuli more salient and powerful than natural environmental stimuli¹⁶.

Activation of the “reward circuit” by psychoactive drugs leads to a feeling of pleasure and euphoria, referred to as “liking” of the drug. However, according to the incentive sensitization theory, repeated drug stimulation of the reward circuit will lead to neuroadaptation and tolerance to the drug (decreasing effect of a given dose) with less reward effect^{12,13,17}. Simultaneously, the incentive motivation to get the drug (craving) increases, resulting in less “liking” and stronger “wanting”^{18,19}. With prolonged sensitization of the reward system, the motivational changes are maintained (“learned”) through modifications of transcription mechanisms regulating the gene expression in the brain’s reward system. This may have long-lasting effects even after prolonged abstinence from the drug, which may explain why addictive behaviours tend to relapse¹⁸⁻²⁰.

The drug dependence syndrome is in ICD-10⁴ defined as “a cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.”

Addictive drug behaviour is thus characterized by “difficulties in controlling its use, persisting in its use despite harmful consequences” and is “fundamentally about compulsive behaviour”²¹. The dependent individual continues drug-taking in spite of awareness of the harmful consequences and a desire to stop drug-taking. It is essential to keep this compulsive character of addictive drug behaviour in mind in the study of health-related risk-taking and drug-related morbidity among problem drug users.

The opioid system

Opioids constitute a group of substances acting on opioid receptors^{12,13}. Within the opioid group are opiates, the natural alkaloids found in the dried latex from the opium poppy (*Papaver somniferum*) called opium; e.g. morphine. Substances synthesized from these alkaloids, such as heroin and oxycodone, are sometimes classified as opiates, other times simply as semi-synthetic opioids. Substances acting on opioid receptors but not derived from opiates are classified as synthetic opioids; this group contains several sub-categories and includes a great number of substances with medical use. Finally, the body produces several substances acting on the opioid receptors, as endorphins and enkephalins, categorised as endogenous opioids²².

Opioid effects

Opioid receptors are found in the central nervous system (CNS), the peripheral nervous system, the gastrointestinal tract and within cells of the immune system^{22,23}. There are three main types of opioid receptors (delta (δ), kappa (κ) and mu (μ) with several subtypes) that show characteristic patterns of distribution and mediate various biological effects. The μ -receptor mediates most of the analgesic effects and also contributes to the adverse effects of sedation and respiratory depression and plays a key role in development of opioid dependence¹².

Opioids have unique analgesic qualities, which make them indispensable in modern medicine. Besides, opioids have a wide range of effects and side-effects²⁴. Among these effects are sedation, euphoria, suppression of coughing and an anti-diarrhoea-effect due to reduced GI-mobility. The most severe adverse effects are respiratory depression, and risk for development of tolerance and dependence.

Heroin

Heroin (diacetylmorphine) is the most frequently used illicit opioid drug. When taken orally, it undergoes a first-pass effect and is metabolized into morphine. After systemic administration heroin has a very short half-life in blood, less than 10 minutes in humans²⁵ and is very quickly metabolized into the active metabolite 6-monoacetylmorphine (6-MAM) with a half-life of 30 minutes²⁶ which is further metabolized into morphine and its active metabolite morphine-6-glucuronide. Both morphine and 6-MAM pass the blood-brain barrier easily, unlike heroin. Heroin thus acts as a prodrug, and its pharmacological effects are mediated through its active metabolites 6-MAM and morphine. Both morphine and 6-MAM have opioid effects, but recent studies identify 6-MAM as the metabolite mainly responsible for the acute heroin effects^{26,27}. Heroin has a very strong ability to induce dependence and this, combined with the harmful effects related to respiratory depression (risk of fatal overdose) and non-medical injecting, is why heroin, especially when injected, is regarded as the most harmful of illicit drugs²⁸.

1.3 Mortality and health problems related to opioid dependence

Dependent opioid users suffer increased physical and mental health problems²⁹⁻³³, partly related to the adverse toxic effects of the drugs, partly to the preparation of drugs and the route of administration and partly due to problematic general life conditions³⁴⁻³⁷. This brief survey will focus on the somatic comorbidity of opioid dependence.

Mortality

Illicit drug use and its related comorbidity may be regarded as an epidemic with specific historical and regional characteristics. Mortality rates are heavily influenced by what kind of illicit drugs and what route of drug administration are dominating within a country or a region. Drug-takers learn their drug habits and preferences from other drug users and the drug use patterns within delimited drug cultures are rather resistant to change and tend to stay

stable over time³⁸⁻⁴⁰. Further, death rates are influenced by characteristic national or regional disease patterns among drug takers and in particular among drug injectors. Especially prevalence of human immunodeficiency virus (HIV) varies much between parts of the world and within regions, e.g. within Europe^{2,3,41}. Finally, the epidemic is characterised by the interaction between the epidemic phenomenon (illicit drug use and related problems) and the societal and ecological responses. Hence, estimations and interpretations of drug-related mortality and comparison between countries and regions within countries are combined with considerable methodological challenges and should be interpreted with caution⁴².

Nevertheless, illicit drug use is indisputably associated with increased mortality^{43,44}. In the year 2000, 197 000 persons (74% male) died of causes attributable to illicit drug use⁹. Based on data from the major cohort studies until 2007, the mean age at death was estimated to approximately 30 years. Standardized mortality ratios (SMR), i.e. the age-adjusted ratio between mortality in a specific group compared to the entire population, vary between 5 and 30. More men than women develop drug dependence, which is the main reason why men dominate among drug-related deaths. Mortality rates among drug dependent males are slightly higher than in the similar female group⁴³. The gender specific SMRs, however, are markedly higher for dependent women reflecting the lower baseline mortality among women in the examined age groups of interest⁴⁵⁻⁴⁸. Predictors of mortality are drug class, injecting drug use, polydrug use (especially heavy alcohol use and benzodiazepine use in combination with opioids), increasing age, length of illicit drug use, not receiving treatment, poorer somatic and mental health and poorer social functioning^{43,44,49-52}.

Problem opioid use and especially injecting of heroin is associated with the highest mortality. Cohort studies comparing death rates between drug classes, consistently find higher death rates among primary opioid users^{43,53-57}. In a recent meta-analysis based on 58 prospective studies reporting mortality rates in opioid-dependent samples Degenhardt and colleagues reported a pooled all-cause crude mortality rate (CMR) of 2,1 per 100 patient years (95% confidence interval (CI) 1.9 – 2.3) and a SMR of 14.7 (95% CI 12.8 – 16.5). Men had higher CMR and lower SMR than women and out-of-treatment periods had higher mortality risk than in-treatment periods, with a pooled relative risk of 2.4 (95% CI 1.8 – 3.2). Overdose was the most common cause of death and death rates increased with the proportion of sample injecting⁴⁴.

In Norway, the majority of problem heroin users inject the drug⁵⁸. In 2008 it was estimated that 67% of all problem heroin users injected only, 15% smoked only and 18% combined smoking and injecting⁵. This is probably one of the main reasons why overdose mortality rates are high in Norway. With a peak in 2001 of 405 drug-related deaths, the number has stabilized around 250 the last years, still one of the highest drug-related mortality rates in Europe⁵⁹. Crude mortality rate at a HIV test centre for IDUs in Oslo 1985 – 1991 was found to be 2.4 per 100 person years, and the standardized mortality ratio was 31⁶⁰. A 20-year prospective study of mortality and causes of death among all hospitalized opioid addicts treated for self-poisoning or admitted for voluntary detoxification in Oslo 1980-81 showed an overall SMR of 23.6. Fifty-three per cent of the deaths were classified as due to “drug dependence”. SMRs were 5.4 for cardiovascular diseases, 4.3 for cancer, 13.2 for accidents, 10.7 for suicides and 28.6 for other violent deaths showing an increased risk of death also for reasons other than overdose. For “other diseases” including drug dependence and overdose the SMR was 65.8⁶¹.

Opioid overdose

Overdose is the most frequent cause of death among problem opioid users and most overdoses are due to heroin.

Mechanism of overdose

The primary mechanism of death and health damage in opioid overdose is opioid-induced respiratory depression leading to hypoxia and death⁶². Hypoxia may cause fatal ischemic damage to the brain and other organs⁶³, and may in non-fatal overdoses cause permanent sequelae from the CNS⁶⁴. Nerve entrapment and ischemic lesions to muscle tissue in the limbs, resulting in peripheral paralysis of varying permanence and necrosis of muscle tissue (rhabdomyolysis), sometimes accompanied by renal failure, are frequent complications to non-fatal overdoses⁶⁵.

Toxicology

Used as analgesic medications in proper professional settings, opioids are relatively non-toxic. It is the way in which dependent opioid users use the drugs that is the main cause of opioid-related health damage, not the drugs as such.

Polydrug use is of great importance in relation to opioid overdose. Alcohol is the most common concomitant drug and is found in half or more of the fatal cases^{43,44,66-69}. Benzodiazepines are found in up to a quarter of fatal cases^{50,67,68}. Alcohol and benzodiazepines are also closely connected to methadone and buprenorphine related deaths⁶⁹⁻⁷¹.

Route of drug administration

Heroin is injected, smoked (“heroin chasing”) or snorted. Overdose risk is greatest when the drug is injected due to the intravenous bolus effect to the brain, and considerably less when smoked^{41,72,73}. Injecting also plays a significant part in methadone and buprenorphine related overdose, and deaths due to these drugs are often related to high concentrations following injection of oral preparations of these long-acting opioids^{70,74-76}.

Tolerance

Opioid tolerance disappears relatively quickly when opioid intake ceases^{12,13}. Several observational clinical studies have demonstrated that dependent opioid users temporarily abstinent during imprisonment experience increased risk of fatal overdose the first weeks after release⁷⁷⁻⁷⁹. A similar situation occurs immediately after opioid detoxification⁸⁰ or after discharge from inpatient non-maintenance addiction treatment^{68,81-83}.

Demography and epidemiology

Most overdose fatalities occur among heroin users with long-lasting drug careers⁴⁴ that are not in treatment at the time of overdose^{48,66,67,81,84}. About three to five per cent of all heroin overdoses are fatal according to Australian estimations⁸⁵, hence the risk of dying from an opioid overdose can partly be seen as dependent on the number of risk situations (non-fatal overdoses) a person has encountered, i.e. as a question of cumulative risk. Further, some studies measuring morphine concentrations in autopsy hair samples report lower morphine concentrations than in persons with ongoing heroin use indicating less frequent heroin use prior to the fatal overdose^{86,87}, or periods of opioid abstinence immediately prior to fatal overdose^{68,88}. Overdoses due to methadone and buprenorphine show the same age profile and most such cases occur among patients not in maintenance treatment at the time of overdose indicating diversion from OMT programs^{66,81,84,89-91}.

Microbial infections related to problem opioid use

Problem opioid users, and especially those injecting heroin or dispersed opioid tablets, are prone to a wide range of microbial infections – which are among the most common and severe complications to problem opioid use^{23,92,93}. A description of specific characteristics concerning infections among problem opioid users is given below.

Pathogenesis

Infections within this group are to a great extent complications to non-medical injecting^{23,92-95}. Intravenous injecting is usually preferred and most frequent, but injecting drug users often lack veins fit for injecting and consequently inject intramuscularly or subcutaneously (“skin-popping”). This practise is associated with increased risk of skin infections compared to intravenous injecting⁹⁶. Opioid users lacking superficial veins viable for injecting frequently use deep veins in the groin and neck, both sites vulnerable for severe infections^{97,98}.

Among drug users the commensal flora often serves as a reservoir for numerous potential pathogens which cause most of the bacterial infections within the group. Common bacteria like *Staphylococcus aureus* and *Streptococcus* species, especially Group A (GAS) may cause local and severe invasive infections and are the most common pathogens, followed by anaerobic cocci and Gram negative rods^{92,93}. In countries where meticillin resistant *Staphylococcus aureus* (MRSA) are common, these have been found to cause abscesses as well as invasive infections⁹². Licking of needles or skin before injecting may cause potential pathogens in the orodental flora to penetrate the skin and provoke local or systemic infections⁹⁹.

Sharing of needles and syringes is the main route of transmission of bloodborne viral infections, such as HIV, hepatitis B and hepatitis C within this group¹⁰⁰⁻¹⁰². Common use of other forms of paraphernalia such as spoons for cooking and cotton filters may also be of importance¹⁰³. Not only bloodborne viral infections but also bacterial infections such as *Staphylococcus aureus*/MRSA¹⁰⁴ may be transmitted via this route.

Drug concomitants and adulterants

During the preparation and the distribution process, heroin may be diluted with adulterants and/or contaminated with microbial agents. Especially clostridial infections are spread in this way and are also associated with “skin popping”⁹³. These are rare conditions, but may be very

severe. Tetanus outbreaks among IDUs have been reported from several countries and are often associated with poor outcome and have been related to contamination of street heroin by tetanus spores. **Error! Reference source not found.** Several outbreaks of wound botulism have been linked to contamination of black tar heroin with botulism spores¹⁰⁵⁻¹⁰⁷. Necrotizing fasciitis caused by clostridial infection have been reported^{93,108}. An extensive outbreak of severe soft tissue infection due to clostridial infection (*Clostridium novyi*), linked to contaminated heroin, occurred in Scotland in 2000, with concurrent outbreaks and spreading in other European countries, also Norway¹⁰⁹. Cases of anthrax due to heroin contamination have occurred, also in Norway¹¹⁰, and a severe outbreak took place in Scotland in 2009 with 31 cases and 11 deaths¹¹¹.

Host susceptibilities

Marginalized living conditions like homelessness or low-standard and overcrowded housing conditions may increase the risk for contagious diseases. Poverty, ongoing drug-taking, poor dental health and lack of nutritious food may lead to malnutrition and related health problems. Polydrug use and generally high levels of somatic and mental comorbidity together with poor living conditions often lead to a reduced general state of health⁹². The oral cavity may also, because of poor dental status, be a specific entry port for systemic bacterial infections in this group¹¹². The process of ageing is often accelerated among dependent opioid users and early aging increases susceptibility to severe infections^{113,114}.

Increased vulnerability to infections may also be related to specific high-risk lifestyles. Having unprotected sex with multiple partners and prostitution may increase the risk for sexually transmitted diseases¹¹⁵.

Clinical manifestations

Local skin infections, especially abscesses, are the most common complication to non-medical opioid injecting and are caused by pathogens within the commensal skin and oral flora^{92,93}. Haematogenous seeding or less often local expansion from delimited superficial infections may cause localized infections e.g. in the skeletal system like osteomyelitis and intervertebral discitis. Intramedullary abscesses and bacterial/septic arthritis are other examples of severe bacterial infections due to septic embolism⁹². Such severe infections may in part be related to injecting in high-risk areas like the jugular and femoral veins.

Non-medical injecting in superficial veins is associated with complications due to vein damage and extravascular drug administration. This may cause deep venous thrombosis and lung embolism as well as endovascular infections. Thrombophlebitis may cause sclerosis of superficial veins leading to injecting in deep veins in the groin with increased risk for deep venous thrombosis¹¹⁶ and septic thrombophlebitis¹¹⁷ or in jugular veins associated with risk for neck and intracerebral complications¹¹⁸. Infective endocarditis, septic thrombophlebitis, mycotic aneurysms and sepsis are among the most severe complications to non-medical injecting⁹². Endocarditis may be both right- and left-sided¹¹⁹ and the left-sided variant may cause septic embolization leading to abscesses e.g. in the brain and spleen. Infective endocarditis related to injecting drug use may be polymicrobial¹²⁰.

Pneumonia and other deep respiratory infections are common in problem drug users. Community acquired pneumonia is most often caused by the same bacteria that causes pneumonia in patients not using drugs, like *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Staphylococcus aureus*^{92,94,95}. Aspiration pneumonia caused by oropharyngeal flora is often related to non-fatal overdoses^{94,95}. Septic embolism may cause pneumonia and lung abscesses^{98,121}. Such infections are often severe and necessitate hospitalization. Opportunistic pulmonary infections like tuberculosis are often associated with HIV infection and are a severe and frequent problem among problem drug users in parts of the world⁹².

Infections with bloodborne viruses transmitted by sharing of drug paraphernalia are frequent among injecting drug users. HIV infection is common among IDUs in many countries, but is relatively rare in other countries like Australia and Norway^{100,122,123} while hepatitis B¹⁰² and hepatitis C^{93,124} are common worldwide. In Norway, the hepatitis C virus (HCV) antibody prevalence among IDUs is assessed to be about 70-80%¹²⁵ and about 2/3 of these are HCV polymerase chain reaction (PCR) positive¹²⁶. Systemic fungal and parasitic infections are rare but severe complications to injecting drug use in patients with or without coincidental HIV infection^{93,127}.

1.4 Effects of opioid maintenance treatment

Opioid maintenance treatment (OMT) was introduced in the United States of America (US) in the mid-sixties¹²⁸ and is presently the most widely used treatment for opioid dependence worldwide¹²⁹. The rationale behind this treatment is that the opioid system in dependent

opioid users may be stabilized by continuous supply of high doses of long-acting opioids like methadone and buprenorphine. The neuroadaptation and dependence-related CNS changes are maintained¹³⁰, but with stable high-dose supply of the long-acting opioid, the patient reaches a steady state without withdrawal or intoxication symptoms. The craving for opioids diminishes and use of illicit opioids will stop or at least decrease. Thus, OMT does not cure the opioid dependence but may reduce many of its harmful effects and give patients an opportunity to benefit from social rehabilitation measures.

OMT is in Norway called “medication assisted rehabilitation” emphasizing that medication is part of a broader rehabilitation programme. OMT was started as a nationwide treatment programme in Norway in 1998. From the start the programme was high threshold, with social rehabilitation as the explicit goal of treatment. The treatment has been high-dose and methadone and buprenorphine are used as maintenance medications. Gradually the aim of the treatment has shifted from “primary social rehabilitation” towards a combined rehabilitation and harm-reduction goal. In the national OMT guidelines from 2010 this is formulated as follows: “to help the patient to achieve his or her optimal functional level”¹³¹. Retention in treatment is high compared to most other countries, but ongoing use of prescribed and illicit benzodiazepines and cannabis is considerable, while use of central stimulants and illicit opioids and non-medical injecting is low^{132,133}.

As described above, dependent opioid users and especially those injecting heroin, suffer a wide variety of health problems. Moreover, the IDU population is also a risk group and a “reservoir” for epidemic diseases like HIV/AIDS and hepatitis B and C. Due to social and mental problems dependent opioid users may be hard to reach and consequently often do not receive appropriate acute care and follow-up for their health problems¹³⁴.

How then, does OMT influence these health problems? When compared to no treatment or non-substitution treatment, reduced use of illegal opioids and less injecting^{135,136}, reduced risk-taking behaviour related to blood-borne viral infections during OMT¹³⁵ and increased retention in treatment¹³⁶ are established in meta-analyses based on randomised controlled trials (RCTs). Reduced mortality and criminal activity during OMT have not been shown in meta-analyses based on RCTs. However, in cohort studies from several countries substantial reduction in mortality in versus out of treatment has been documented^{41,50,51,91}. In 1996 Caplehorn and colleagues⁵⁰ estimated the risk of death to a quarter during OMT treatment

compared to out of treatment based on studies from the US, Sweden and Germany. Concerning the Norwegian OMT programme, Clausen and colleagues have documented reduced mortality during OMT⁸⁹ and Bukten and colleagues reductions in criminal activity¹³⁷ in national cohort studies.

Improved somatic health during OMT has been reported in some studies based on interviews¹³⁸ and clinical assessment¹³⁹ and reduced inpatient care due to infections during maintenance treatment has been found¹⁴⁰. Still, few studies have examined OMT-related somatic health effects and changes in morbidity patterns¹⁴¹. Especially, the knowledge about changes in morbidity and health care consumption when dependent opioid users enter maintenance treatment is scarce. As increased health problems are among the most severe consequences of opioid dependence and problem opioid use, investigation of health effects related to maintenance treatment is strongly warranted.

2 Objectives

2.1 Overall research aims

The overall aim of this thesis was to investigate the effects of OMT on acute and subacute somatic comorbidity among dependent opioid users. The term somatic comorbidity was used because the fundamental health problem defining the target group was opioid dependence. In Paper 1, all acute and subacute somatic disease incidents leading to inpatient or outpatient hospital contact, contact with general practitioners (GPs) or emergency wards were examined. The study sample was 35 OMT patients in one Norwegian municipality, Gjøvik. In Paper 2 and Paper 3, only inpatient and outpatient hospital contacts were considered. The study sample was 200 OMT patients from two Norwegian counties, Hedmark and Oppland. The focus in both studies was delimited to acute and subacute incidents, chronic somatic diseases were not assessed unless they led to acute/subacute incidents. Further, in Paper 2 and Paper 3, the impact of patient characteristics on rates of different kinds of disease incidents was estimated.

2.2 Objectives for each paper

Paper 1: The objective was to compare health care utilization due to acute and subacute somatic disease during versus out of maintenance treatment in a cohort of OMT-patients. The hypothesis was that health care consumption would decrease during OMT due to less morbidity as a consequence of reduced illicit drug use and injecting. Additional research questions were: if such reduction does occur, is it valid only for patients who stay abstinent from illicit drugs during OMT or also for those with ongoing drug-taking? And, is there a shift in the relative distribution of drug-related and non-drug-related treatment episodes during OMT compared to out of treatment? Finally, does the relative distribution of type of health care contacts (GP versus hospital) change between in- and out-of-treatment periods?

Paper 2: The objective was to investigate how acute/subacute somatic comorbidity varies before, during and after maintenance treatment (in the paper and the thesis referred to as OMT status). The main hypothesis was that somatic morbidity is reduced during treatment and more detailed research questions were: what changes in somatic morbidity are found during OMT compared to before and after treatment, and what kinds of disease incidents are reduced? And,

how do various patient characteristics influence the effect of OMT-status on somatic morbidity?

Paper 3: This paper focused on acute/subacute somatic morbidity after interruption of maintenance treatment. Important pre- and during-OMT characteristics were compared between patients with and without interruption of maintenance treatment including the pre-OMT rates of various kinds of acute/subacute hospital-treated disease incidents. Further, the distribution of such incidents throughout the post-treatment period was examined. The research questions were: Do patients with interruption of OMT differ from non-interrupters regarding pre- and during-OMT characteristics, indicating increased risk-taking behaviour? And, how does the incidence of acute/subacute somatic health problems vary according to OMT status (before, during and after treatment) and especially throughout the post- OMT period within the group of OMT interrupters?

3 Material and methods

The thesis consists of two studies. Both studies are observational with a longitudinal cohort design. Paper 1 relates to the first study, while Paper 2 and Paper 3 relate to the second study. Methods and material for each study is described below.

3.1 Study 1 (Paper 1)

Sample and setting

Record information from hospitals and from GPs and emergency wards was gathered retrospectively. Information on ongoing drug-taking was drawn from the annual status reports within the national OMT programme from 2001 onwards, thus these data were prospective. This information was collected with informed consent from all participants.

The cohort was established in 2004-5 and consisted of patients from one municipality (Gjøvik) in Oppland County, Norway, who were admitted to OMT for the first time between 1999 and June 2005. By the end of 2005, all 40 patients who had started OMT were still alive and in treatment, and 36 consented to participate. Data were not collected for one person, rendering 35 participants and a participation rate of 87.5%.

Data sources

Interview

Thirty-two of the 35 participants (92%) were interviewed about somatic disease incidents before and during OMT, and during out-of-treatment periods. The first author (IS) performed all interviews, which were conducted in a GP centre or in the patients' homes.

Medical records

Records from emergency wards and somatic departments in local hospital were gathered for all participants. Based on interview information about hospital treatment, records from other hospitals where the participants reported to have received medical treatment during the observation period were requested and all these records were received. All records underwent full-text in-depth examination by IS. Ninety-one per cent of requested records from GPs who were or had been the patients' regular GP during the observation period were collected.

Annual status reports from the national OMT programme

For 31 patients (89%) information about ongoing use of illicit drugs and alcohol during OMT, based on urinary testing and clinical assessment, was gathered from the annual reports made for each OMT patient in Norway since 2001. The annual report scores overall drug use during the last four weeks on a five-point scale. In our study we simplified this to a dichotomized score for the entire treatment period, differentiating between “problematic” use with severe consequences for psychosocial function and “abstinence and non-problematic use” without such consequences.

Outcome measures and observation period

The outcome measures were incidence rates during the in-OMT and out-of-OMT periods of acute and subacute somatic disease incidents documented in records from GPs, emergency wards and somatic hospital departments. Observation time before and between treatment periods were combined as the out-of-treatment period, referred to as “before OMT” in the paper, and was defined as the last five years out of treatment (before the first admittance to OMT or between treatment periods). Only three of 35 patients had experienced interruption of OMT (in total five years), thus “out-of treatment” time was mainly before OMT. As all patients were in maintenance treatment at study end-point, there was no “after-OMT-time”. The during-OMT period was defined as the first five years during maintenance treatment in one or consecutive periods.

Only incidents documented in records were included. Health care contacts due to follow-up of chronic disease were not counted, but acute/subacute incidents caused by an underlying chronic disorder were counted as a new incident. An incident registered in several records was counted as one incident. One incident could lead to more than one contact. Incidents were categorised as drug-related (overdoses, injecting-related or other drug-related) or non-drug-related (infections, injuries, other). Inpatient treatment days and number of outpatient hospital contacts were also registered.

Inter-rater agreement

Inter-rater agreement was estimated according to Cohen’s kappa. The inter-rater reliability on whether hospital treatment episodes were drug-related or not ($\kappa = 1$) and if drug-related, to

which category (overdose, injecting-related or other) each episode belonged ($\kappa = 0.82$), was good.

Statistics

Wilcoxon signed rank test was used to compare incidence rates during the in-treatment and out-of-treatment periods. Pearson chi-square test was used to examine changes in the relative distribution of drug-related and non-drug-related incidents during the in- and out-of-treatment periods. Fischer's exact test was used to assess changes in acute health problems during treatment versus ongoing drug- and alcohol use during OMT. Pearson chi-square test was used to compare changes in type of health service contact (GPs versus hospital) in versus out of treatment.

Ethics

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services.

3.2 Study 2 (Paper 2 and Paper 3)

Sample and setting

Record information from hospitals was gathered retrospectively. Information on ongoing drug-taking, overdoses during OMT and reasons for OMT interruption was drawn from the annual status reports within the national OMT programme. This information was gathered with informed consent from all participants. Information on patient characteristics was gathered from a structured interview (Appendix 1).

The cohort in Study 2 was established in 2007-8 and consisted of OMT patients from Oppland county and parts of Hedmark (the municipalities Ringsaker, Hamar and Stange) county. The eligibility criteria were 1) having started OMT for the first time between January 1998 and the end of June 2007 in this area or continued OMT after having moved into the area during this period, and 2) having contact with or being known by local health or social services at the time of invitation. Information about eligibility criterion 1) was based on register information from the national OMT programme. The identity of patients was unknown to the research group until consent was obtained; participants were recruited by personnel in local health and social treatment services and pharmacies.

Out of a total of 319 persons who had started or continued OMT in this area (criterion 1), 38 had no contact with and were unknown to local health or social services (criterion 2) and assessed ineligible for the study. Among the 281 eligible, 13 who had died before the study was started, were included. Among the 268 eligible alive, 187 consented to participate, 81 did not, and hence the cohort consisted of a total of 200 persons. The participation rate was 71.2%, 68.8% among patients in treatment versus 73.7% among those not in treatment when recruited. Fifty-one (25.5%) had experienced interruption of OMT at least once (12 more than once), and this subgroup is the focus of Paper 3, while the whole cohort is studied in Paper 2.

Data sources

Three data sources were used: a structured interview, medical record data and data from the annual status report on each patient from the national OMT programme.

Interview

One-hundred-and-thirty-six out of the 187 participants still alive (73%) underwent a structured interview with questions on demographic data and education and employment history, former hospital treatment and recent drug taking and drug trajectories (modules from the EuropASI questionnaire). The interviews were performed by IS (54%) and three students (46%) from the University of Oslo. Eighty-five per cent of the interviews were performed face to face; 30% by home visits, 29% in different kinds of public institutions (inpatient treatment centres, low-threshold day-care centres for drug users, GP offices, prisons), 26% at other meeting points (e.g. outdoors in parks or in cafes) and 15% were interviewed by telephone. Fifty-one of the participants were not interviewed, some of these were impossible to reach by telephone or home visits, and some did not show up on repeated appointments.

Medical records

In study 1 (Paper 1) between 80 and 85% of all somatic disease incidents that were documented in records and assessed as severe lead to hospital treatment during the in-treatment as well as out-of-treatment periods. Hence, in Study 2 only records from somatic hospital departments were examined and this was assessed as sufficient to evaluate changes concerning severe somatic morbidity according to OMT status (before-during-after OMT). Records from somatic departments in the local hospitals (Innlandet Hospital, which is a hospital trust comprising all the hospitals in the two counties Hedmark and Oppland) were gathered for all participants. Based on information from these records and from the interview,

records from other hospitals where the participants had received treatment, were requested. More than 99% of all requested records were gathered and examined. All records underwent full-text in-depth examination by IS.

Annual status reports from the national OMT programme

Data on ongoing drug-taking during OMT were based on data from the annual status report. A combined score for polydrug use (illicit/non-prescribed use of opioids, cannabis, benzodiazepines and central stimulants) for the whole during-OMT period was estimated based on urine tests and clinical observation. Dates for admission to and exit from OMT were also drawn from these reports which were available for 183 participants (92%).

Outcome measure

The outcome measures in Study 2 were incidence rates of acute/subacute somatic disease incidents leading to inpatient or outpatient hospital treatment and rates of inpatient days and outpatient hospital treatment contacts. As OMT status is a time varying variable, rates were estimated according to OMT status, i.e. before, during and after OMT. In Paper 2 and Paper 3 the disease incidents are referred to as “hospital-treated episodes”, “treatment episodes” or just “episodes”. Only episodes documented in hospital records were included. The number of treatment episodes and the number of inpatient days and outpatient hospital contacts due to these episodes were recorded. Health care contacts due to chronic disease were only included if the disease caused an acute incident. Each incident was only registered once even if it was registered in records from several hospitals. Incidents were categorised into three main groups: drug-related (overdoses, injecting-related and other drug-related incidents), non-drug-related (infections and others) and injuries. Injecting-related incidents were divided into the subgroups deep venous thrombosis/lung embolism, acute hepatitis B and C, local bacterial infections, systemic bacterial infections and other injecting-related incidents. Other drug-related incidents were divided into the subgroups withdrawal-related, impaired general health condition, neuromuscular (e.g. rhabdomyolysis or peripheral neural damage) and any “other drug related episode” (not overdose or injecting-related).

Predictors (patient characteristics)

The main focus of Study 2 was to examine the impact of maintenance treatment on the incidence rates of hospital-treated acute/subacute somatic disease incidents, i.e. to compare rates in the periods prior to, during and after OMT.

In Paper 2 interaction (or effect modification) between OMT status (before versus during and after versus during OMT) and the following variables were tested: gender, age at OMT start, age at heroin debut, years of opioid dependence before OMT start, years of education, years of employment, lifetime number of overdoses, having experienced OMT interruption and ongoing use of illicit drugs during OMT.

In Paper 3 the following patient characteristics were tested for interaction with incidence rates the first post-OMT year versus the pre-OMT period for the group with interrupted treatment: gender, age at OMT start, years of employment and education, overdoses during life and during OMT, taking or not taking illicit drugs when leaving OMT, illicit drug-taking during OMT and having experienced more than one OMT interruption.

Observation period

The pre-OMT period was defined as the five years previous to the first admission to OMT and the during-OMT period as the first five years during maintenance treatment in one or consecutive periods. The post-OMT period was defined as the first five years out of treatment after the first OMT admission in one or consecutive periods. In Paper 3 post-OMT treatment episodes were registered according to the end of the preceding treatment period and divided into different post-OMT periods: month one, months two and three, months four to twelve, and year two to five ("later post-OMT period"). The total pre-OMT observation time was 1000 patient years (255 patient years among participants with interrupted treatment), 813 patient years during OMT (193 among participants with interrupted treatment) and 91 patient years after interruption of treatment. The study end-point for each patient was defined as the date when the record from the local hospital was collected during 2008/2009.

Inter-rater agreement

Inter-rater agreement was established in Study 1 (see above). In Study 2 IS scrutinized all full-text records. Treatment episodes considered problematic to categorise were discussed between IS and another physician (co-author ER) until consensus was reached.

Statistics

Incidence rates were analyzed by means of a Poisson regression model. Dependencies in the data, due to the fact that each participant is measured repeatedly (before – during – after OMT), were handled by Generalized Estimating Equations with unstructured working correlation and robust variance estimation. With regard to drug-related hospital treatment episodes, the possible influence of different patient characteristics on the effect of OMT was investigated by including the interaction between OMT and the characteristic in question in the model, one by one. Incidence rate ratios with 95% confidence intervals were estimated. The significance level was set to 5%. Pearson Chi-Square test (categorical variables) and Independent-Samples T-test (continuous variables) were used to compare patient characteristics between patients with and without interruption of OMT. All analyses were performed in SPSS (version 15, SPSS, Chicago, Ill., USA).

Ethics

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. Exemption from professional secrecy duty of confidentiality for those dead was given by the Norwegian Directorate of Health.

4 Results

4.1 Paper 1

Paper 1 focuses on differences in somatic health care utilization and morbidity between periods in and out of (before and interruption periods) maintenance treatment in a cohort of 35 OMT patients.

The gender distribution was typical for illicit opioid users, 63% were male. Age at OMT start was high (37 years), treatment was high dosage, predominantly with methadone. Nearly all participants had HCV antibodies, reflecting injection as the main heroin administration route. None had antibodies against HIV.

Two-hundred-and-seventy-eight disease incidents were registered. There was a reduction in the total number of incidents treated in hospitals, by GPs or emergency wards by 35% ($p = 0.004$) during OMT. Substance-related incidents were reduced by 62% ($p < 0.001$) and among these, injecting-related incidents by 70% ($p < 0.001$), while non-fatal overdoses did not show statistically significant reductions ($p = 0.13$). Non-substance-related incidents were unchanged ($p = 0.74$). Overall inpatient days were reduced by 76% ($p = 0.003$) while outpatient hospital treatment contacts showed a non-significant reduction of 46% ($p = 0.06$). Incidents were less often related to substance use during OMT, 36% compared to 62% out treatment ($p < 0.001$).

Forty per cent of all disease incidents during OMT were documented exclusively by GPs, compared with 25% in the out-of-OMT period ($p = 0.02$). Around 90% of all hospital treatment, out of as well as during OMT, took place at the local hospital in Gjøvik. Between 80 and 85% of all disease incidents assessed as moderate or severe led to hospital treatment and were documented in hospital records during as well as out of maintenance treatment (this finding is not referred in the paper).

Changes in rates of treatment episodes between in-treatment and out-of-treatment periods were compared for nine patients with and 22 patients without problematic substance use during OMT. Reduction in injecting-related incidents did not differ significantly between the groups. The overall reduction in substance-related treatment episodes was greater for patients without problematic drug use, but the finding was not significant in this small sample ($p =$

0.06). The reduction in overall treatment episodes was significantly greater for patients without problematic drug use ($p = 0.007$).

4.2 Paper 2

Paper 2 focuses on acute and subacute morbidity before, during and after maintenance treatment. Six-hundred-and-five treatment episodes were identified before OMT, 310 during and 106 after interruption of maintenance treatment. Patient years at risk were 1000 before, 813 during and 91 after OMT.

The gender distribution was typical for dependent opioid users, $\frac{2}{3}$ being male. The age at OMT start was high (37 years) and the long mean duration (12 years) of opioid dependence before the first OMT admittance reflects the late start of OMT in Norway, with an accumulated need for treatment among older dependent opioid users when the program was launched. Sixty-seven per cent started with methadone when included in OMT and methadone dosage was high (122 mg). One fourth of both male and female participants had experienced interruption of maintenance treatment once or more, 12 more than once.

Total hospital-treated episodes were reduced by 37% during OMT compared to the period before the first admission to treatment and doubled after treatment interruption compared to the in-treatment period. Inpatient hospital treatment days were 38% lower and outpatient hospital treatment contacts 27% lower during compared to before treatment. After treatment the rate of inpatient days was 5.1 times higher than during treatment and the rate of outpatient treatment contacts were 2.6 times higher. All these findings were statistically significant.

Drug-related episodes were reduced by 76% during versus before treatment, injecting-related episodes were reduced by 83% and the rate of overdoses was 64% lower than before OMT. Among the injecting-related episodes, local and systemic bacterial infections were the most common. The rate of drug-related inpatient days was 84% lower and the rate of outpatient contacts 79% lower compared to the pre-treatment period. After treatment interruption drug-related episodes were eleven times more frequent than during treatment. These findings were also statistically significant.

Non-drug-related episodes were 35% more frequent during treatment compared to the pre-OMT period ($p=0.02$) but did not show significant increase after versus during OMT. Injuries did not show significant changes according to OMT status.

Regarding drug-related episodes three variables (having experienced interruption of OMT, years of employment and duration of opioid dependence before OMT) showed statistically significant interaction (p -value of interaction < 0.05) with OMT status (before versus during OMT), while ongoing drug-taking during OMT showed interaction with OMT status of borderline significance (p -value of interaction 0.07). Patients without interruption of OMT showed greater reduction in drug-related episodes than those with interrupted treatment; however, even among the OMT interrupters the reduction was statistically significant (49%, $p=0.04$). After treatment, drug-related episodes were 5.6 times more frequent than during OMT among the interrupters. More work experience and longer duration of opioid dependence before OMT showed association with greater reduction of drug-related episodes during OMT. Ongoing drug-taking during OMT was associated with less reduction in drug-related episodes during treatment, even so, the quartile taking most drugs showed a significant reduction.

4.3 Paper 3

Paper 3 focuses on acute and subacute hospital-treated somatic disease incidents before, during, and especially after OMT in the subgroup with interrupted maintenance treatment ($N=51$) within the same cohort ($N=200$) as in Paper 2.

None of the pre-OMT patient characteristics tested (gender, age at OMT start, age at heroin debut, years of opioid dependence before OMT, years of education, years of employment and lifetime number of overdoses) differed significantly between the groups with and without interruption of OMT. Contrary to this, OMT interrupters scored significantly higher on illicit drug-taking and overdoses during treatment, indicating “problems in treatment”. Among the interrupters only 15% were assessed as stable and not taking drugs when leaving OMT. Pre-OMT rates for total drug-related and non-drug-related treatment episodes did not show significant differences between patients with and without treatment interruption.

Drug-related treatment episodes were 3.6 times more frequent the first post-OMT year compared to the pre-OMT period. Overdoses were 2.9 times, injecting-related episodes 2.6

times and other drug-related episodes 7.7 times more frequent. Among the injecting-related episodes local skin infections and systemic bacterial infections were most common before OMT and also showed the greatest increase after OMT interruption. Among the other (not overdoses or injecting-related) drug-related episodes (see Table 1, Paper 2 for definition), contacts due to “impaired general health condition” showed the greatest increase. These changes were all statistically significant. The overall increase in drug-related treatment episodes was greatest the first months after OMT interruption and in overdoses especially the first four weeks.

While non-drug-related episodes did not show significant change before versus during OMT, they showed a significant increase the first post-OMT year compared to the pre-OMT period. With regard to post-OMT years two to five (later post-OMT period), there was no statistically significant increase in drug-related or non-drug-related episodes compared to the pre-OMT period. Injuries showed stable rates throughout the whole observation period.

The influence of various patient characteristics on increase in drug-related treatment episodes the first post-OMT year versus the pre-OMT period was tested. An interaction of borderline statistical significance ($p=0.06$) was found between gender and OMT status, men showing greater increase than women (incidence rate ratio (IRR) 5.0 (95% CI 2.8 – 8.9) versus 2.3 (95% CI 1.1 – 4.6)). Age at OMT start, years of employment, years of education, overdoses during lifetime, drug-taking during OMT, overdoses during OMT and having experienced more than one OMT interruption during the observation period did not interact significantly with OMT status. The 15 per cent who were described as leaving OMT voluntarily and not taking drugs at that time did not differ from the rest regarding increase in drug-related treatment episodes the first year after treatment.

5 Discussion

5.1 Summary of findings

Main findings

- Drug-related acute/subacute somatic disease incidents leading to hospital and other health service treatment among dependent opioid users were significantly reduced during OMT compared to before treatment. This comprised overdoses, injecting-related disorders and other drug-related disease incidents.
- This held not only for patients staying abstinent from psychoactive substances during OMT, but also for patients with ongoing drug-taking during treatment as well as for patients with interrupted treatment (Study 2).
- Among patients with interrupted OMT, the incidence of drug-related disease episodes increased significantly after interruption of treatment, especially during the first months. Non-fatal overdoses were most frequent during the first four weeks after interruption of treatment (Study 2).

Other findings

- Non-drug-related somatic disease incidents leading to hospital treatment showed a significant increase during maintenance treatment compared to the pre-treatment period (Study 2). Injuries did not show significant change according to OMT status.
- The proportion of treatment episodes related to drug use was significantly lower during OMT compared to out of treatment (Study 1).
- A significantly greater proportion of health care contacts were by GPs during OMT compared to the out-of-treatment period (Study 1).

5.2 How these studies relate to previous knowledge

The aim of these studies was to examine the impact of OMT on acute and subacute somatic morbidity, i.e. changes in morbidity according to the patients' OMT status (before, during or after OMT). Rates of disease incidents and corresponding rates of inpatient days and outpatient contacts were regarded as proxy indicators for somatic morbidity. How do these studies add to previous knowledge?

Research on OMT-related changes in morbidity among problem opioid users is scarce¹⁴¹. Improvement in somatic health and reduction in heroin use and overdoses during maintenance treatment have been documented in large cohort studies in the US, the United Kingdom and Australia based on interviews^{51,138,142} and a recent metaanalysis documented significant reductions in illicit opioid use, injecting and sharing of injecting equipment during OMT¹³⁵. Reduced consumption of inpatient care due to infections other than HIV during methadone treatment¹⁴⁰ and improved physical health status during the first 12 months in OMT based on clinical assessment¹³⁹ have been documented. However, we could identify no other studies using cohort design based on scrutiny of full-text records to explore long-term changes in patterns of acute somatic morbidity related to OMT status. Our studies show substantial reductions in acute/subacute drug-related morbidity and health care utilization during maintenance treatment and this finding is in accordance with the studies referred to above.

Studies from several countries have documented that injection site infections and severe complications to these are a major problem among IDUs^{94,121,143-148} and that they contribute substantially to hospital utilization and costs related to illicit drug use^{94,145,146}. In our studies we document major reductions in injection-site infections and in systemic bacterial infections during compared to before maintenance treatment. After interruption of OMT we found substantial increase in injecting-related episodes (which mainly are bacterial infections), especially during the first months off maintenance treatment. These infections are often successfully treated through intensive and resource-demanding hospital treatment. Our study demonstrates the importance and scale of these infections and brings new evidence on the extent to which such infections are reduced during maintenance treatment.

In the Australian Treatment Outcome Study (ATOS) Darke and colleagues concluded: “Perhaps the most clinical implication to emerge concerned the importance of *stable retention* in treatment as a consistent predictor of superior treatment outcome” and that “the chances of successful outcome for these (more dysfunctional) clients, however, improve dramatically the longer they can be retained in a stable treatment”¹³⁸. In Paper 2 we showed that the quartile taking most drugs during OMT and probably maintaining the most “addictive” and risk-taking lifestyle, still showed significant reduction in drug-related episodes during treatment, though less than the quartile not taking drugs at all. This implies that even patients maintaining illicit drug use during treatment benefit from OMT. Moreover, even the group with interrupted treatment showed significant reduction – though less than those with continuous treatment –

during compared to before OMT. After treatment the interrupters showed great increase in all kinds of drug-related episodes, especially the first months. As far as we know, the distribution of acute somatic disease incidents throughout the post-treatment period has not been studied before. However, as cited above, Darke and colleagues in the ATOS study found that stable retention in treatment was associated with “superior treatment outcome”. The very high incidence rates of all kinds of drug-related episodes just after leaving treatment in our study, are in accordance with these Australian findings. They are also in accordance with the conclusion in a review article by Magura and Rosenblum¹⁴⁹ concerning experiences on leaving methadone treatment: “Virtually all of these studies (exiting from extended methadone detoxification, “abstinence-oriented” methadone programs, and regular methadone maintenance programs) document high rates of relapse to opioid use after methadone treatment is discontinued. Most of the patients studied left treatment without meeting clinical criteria for detoxification, although high relapse rates were also reported for patients who completed this program. The detrimental consequences of leaving methadone treatment are dramatically indicated by greatly increased death rates following discharge”.

5.3 Treatment implications

Maintenance treatment in Norway is now regarded as a treatment modality for opioid dependence based on high dose opioid substitution with methadone or buprenorphine in a time-unlimited maintenance perspective with a combined social rehabilitation and harm reduction objective organized within the public health- and social care system¹³¹. Before the new guidelines were enforced from 2010, contrasting practices had developed in parts of the country reflecting opposed attitudes on whether a high-threshold social rehabilitation orientation should be the only acceptable basis for treatment or if a harm-reducing perspective should be acceptable, allowing patients with ongoing illicit drug-taking to continue in treatment¹⁵⁰⁻¹⁵³. Even if the new guidelines in several ways have concluded this debate, there might still be disagreements in how to implement them¹⁵⁴. Our findings should have implications on some aspects of how to practise maintenance treatment, both in the Norwegian and in an international context.

OMT significantly reduces acute and subacute somatic morbidity and should be available to dependent opioid users who want to enter the treatment programme. Programmes should be

flexible and organized so as to meet the needs of different groups of dependent opioid users, comprising both harm-reducing and social rehabilitation goals.

OMT should generally be regarded as a time-unlimited treatment, also for patients not reaching stable social rehabilitation. The goal should be to keep patients in treatment, also when they are dysfunctional and engage in high-risk activities. Serial discharges and re-enrolments are particularly unfortunate. Re-inclusion of OMT drop-outs should be prompt and non-bureaucratic when patients are ready for it.

Involuntary discharge from OMT should only be an option if continued treatment is regarded as unsafe for the patient or others, i.e. if continued treatment is assessed to be a greater health risk for the patient than interruption of treatment. The risk for diversion of OMT medications should usually be handled by strengthening the control of intake.

Patients who are well rehabilitated outside drug circles and who have not been taking illicit drugs for long frequently want to taper off maintenance treatment and finally live without substitution medication. But even in this context, coming off the medication is often hard. Patients should be informed about risks and difficulties related to exit from maintenance treatment. If they uphold the decision to leave OMT, they should be closely followed up and assured that they can restart OMT medication rapidly if they relapse.

5.4 Further research

The effect of maintenance treatment on morbidity is still scarcely studied though OMT is the most widely used treatment for opioid dependence and still expanding. Hence, further research is demanded and several topics should be addressed.

As OMT is considered as a time-unlimited treatment, the long-term health effects of receiving high-dose opioid maintenance should be thoroughly examined in long-range cohort studies.

Mortality is reduced within OMT programmes and patients will live longer. Therefore OMT-effects on older patients is an important topic. Dependent opioid users tend to suffer increased chronic health problems and long-term outcome of chronic diseases among OMT patients should be further studied.

Prevalence of mental disorders is substantially increased among dependent opioid users compared to the general population. Inpatient and outpatient treatment for mental disorders in a pre-during-post-OMT perspective is not studied in the thesis and such studies will be of interest.

We found highly increased acute/subacute drug-related morbidity after OMT termination, especially the first months. While overdoses seemed to stabilize on the pre-OMT level from the second post-OMT year on, injecting-related and other drug-related incidents showed a tendency, though statistically non-significant, to stay on a higher level than before the first OMT entry. However, the overall post-OMT patient years at risk in our study was only 91 in a group of 51 patients, and especially the findings from the second year on relates to relatively few observed events. Further studies, focusing both on the period soon after treatment interruption and on the long-term effects of OMT termination should be carried out.

Well rehabilitated OMT patients frequently consider tapering off OMT medication and go after a drug-free life without maintenance treatment. This is understandable, though it may be risky, as opioid substitution is “heavy” medication in an unlimited time perspective, and the treatment is not without side effects. Thus, further long-range research focusing on health, quality of life and relapse prevention especially in well-rehabilitated post-OMT patients is therefore important.

The OMT-related changes in health service expenditures in accordance with the changes in consumption of health care services and especially hospital treatment have not been addressed in this thesis. Studies of OMT-related effects – in a pre-during-post-OMT perspective – on health care costs, not only related to acute somatic morbidity, but also to treatment of substance-use-related mental and behavioural disorders and various kinds of chronic diseases will be of interest.

5.5 Methodological considerations

Choice of cohort design

Randomised controlled trials (RCTs) are often considered to be the “gold standard” when treatment effects are evaluated^{155,156}. Some RCTs have been conducted comparing methadone maintenance treatment with either placebo medication or non-pharmacological treatment for

opioid dependence. In a recent metaanalysis¹³⁶ Mattick and colleagues identified 11 RCTs, two were double blind, with a total number of 1969 participants. The authors conclude: “Methadone is an effective maintenance therapy intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilise opioid replacement therapy. It does not show a statistically significant superior effect on criminal activity or mortality”. Morbidity was not an outcome measure in this analysis.

However, while RCT design is widely accepted as the best way to study the effect of medical (most often pharmacological) treatment for clearly delimited medical conditions, it is not necessarily the most appropriate way to evaluate different treatment modalities for opioid dependence. The scepticism towards RCT design in addiction research is both technical and theoretical¹⁵⁷ and RCT design may also raise severe ethical objections by withholding treatment for a control group¹⁵⁸. Among the technical problems are difficulties to construct a properly matched control group¹⁵⁹ and problems with covert selection prior to randomisation¹⁶⁰. Among the theoretical objections is that RCTs focus on internal validity and efficacy contrary to external validity and effectiveness under “real world” clinical conditions^{161,162} and that the random allocation of participants in an RCT differs fundamentally from the process where patients with complex mixtures of problems through active selection enter the kind of treatment they actively seek^{163,164}.

For these reasons RCT design is not necessarily suitable to evaluate OMT effects when maintenance treatment is compared to non-medication treatment or no treatment. Current knowledge on OMT treatment outcomes is therefore mainly based on observational studies, especially longitudinal cohort studies. Unlike what was found in RCTs, reduced mortality during maintenance treatment is well established based on findings from several cohort studies from various countries^{41,50,89,91}.

When planning this research project, RCT design was no option because of practical and ethical reasons. A cohort design with collection of record data on disease incidents back in time was chosen and all eligible patients who had started OMT between January 1998 and July 2007 were invited. With regard to the date of examination of the records the collection of record data was retrospective. However, as the cohort is basically defined by OMT participation, the date of OMT inclusion or even five years previous to the first admission to

OMT could be regarded as the study starting point. In this perspective data collection could be regarded as prospective and the study could be seen as a “historic prospective” study. As data on disease incidents and drug-taking during treatment were gathered from health service records and the record collection was almost complete, the risk of data loss was minimised.

The cohort consisted of OMT patients and there was no control group. The study objective was to study changes in acute/subacute somatic morbidity when dependent opioid users enter and exit maintenance treatment. Rates of disease incidents and treatment contacts were measured repeatedly in the same individuals before, during and – for those interrupting treatment – after treatment interruption. Hence, the participants were “their own controls”. To set up a matching control group – i.e. a sample of dependent opioid users *not* receiving maintenance treatment and presumed not to deviate systematically from the OMT sample on other characteristics – would out of practical, theoretical and ethical reasons hardly have been possible. Therefore, the chosen “historic prospective” cohort design, with the patients as their own controls, was regarded as the best possible study design.

Poisson regression – estimation of incidence rates and incidence rate ratios

The incidence rate ratio is the effect estimate in Poisson regression. The incidence rate of the kind of event in question is the outcome variable and the incidence rate ratio (IRR) is the ratio between the incidence rates of this event in two different states of a predictor variable.

The main focus in Paper 2 and Paper 3 was to examine the impact of changes in OMT status (before, during and after OMT) on the incidence rates of different types of hospital-treated disease episodes. However, several other patient characteristics (predictors/covariates) could theoretically also have an impact on these rates. OMT status is a time varying covariate as patients go in and out of treatment. To examine the effect of patient characteristics – other than OMT status – with conceivable impact on incidence rates, the observation period was split according to OMT status (before, during and after OMT). The impact of each characteristic in question on the crude rate of all drug-related episodes was then tested by estimating the IRR between different states of each predictor variable, split according to OMT status (before, during and after OMT for OMT interrupters, before and during OMT for non-interrupters) in the Poisson regression model. In addition to OMT status the following patient characteristics were tested (this analysis is not in the paper): gender, having experienced interruption of OMT, years of employment and education, age at OMT start, age at heroin

debut, years of heroin dependence before the first OMT admission, lifetime overdoses and illegal drug-taking during OMT. Only OMT status and lifetime number of overdoses showed a significant impact on the incidence rate ratio of drug-related incidents.

As the primary interest of Study 2 was to examine the influence of maintenance treatment (OMT status) on the incidence rates of hospital treatment episodes, possible interaction between OMT status and the patient characteristics listed in the foregoing paragraph was tested. The results of the interaction analysis were reported in the Results section. Potential confounding was tested for the same variables. No confounding of importance was found, which would be expected as the outcome measure (incidence and treatment contact rates) was registered repeatedly (before, during, after OMT) in the participants.

Selection bias

As the participation rate in Study 1 was as high as 87.5% selection bias was of minor importance in this study. In Study 2 the participation rate was 71.2%, about the same for patients in and out of treatment when invited, and two hundred persons altogether were included. Thirty-eight were assessed as not eligible as they had left the treatment programme and had no current contact with social services. It is conceivable that “problem patients” might be overrepresented in this group and also among the 81 who did not consent to participate. However, as the participation rate for those in and out of treatment when invited was about the same, it is unlikely that this factor should cause considerable bias. In both studies nearly all requested records were obtained. Hence, selection bias was of limited importance and the cohort was considered as representative for the OMT patients in the area.

Acute hospital treatment episodes – a proxy for acute morbidity?

Both studies assessed acute/subacute somatic disease incidents treated by health care services and not morbidity as such. A key question is whether changes in incidence and treatment contact rates according to OMT status (before, during, after OMT) reflect a change in morbidity; in other words whether these rates can be regarded as proxy indicators for morbidity. Information on hospital treatment outside the local area was based on patient recall and some disease incidents prior to treatment may have been overlooked. In addition, there will be a gap between the volume of disease in any patient sample, and what results in health service contacts, and this is particularly so in a population of IDUs¹³⁴. Due to the structure of the treatment program, contact with health services was close during OMT, which probably

increased patients' help-seeking resulting in medical treatment for health problems that would not have been treated outside OMT. Further, the patients were five years older during OMT than in the pre-OMT period, causing an age-dependent increase in morbidity. These three factors – recall bias, changed help-seeking behaviour and increasing age – all tend to increase the volume of observed hospital-treated episodes during treatment compared to before treatment. Despite this, we found significant reduction in treatment episodes during OMT. Hence, our findings most probably reflect a true reduction in acute and subacute morbidity during compared to before OMT.

Non-drug-related morbidity – a true increase during OMT?

Non-drug related hospital treatment episodes showed significant increase during compared to before OMT in Study 2. Theoretically it is possible that the increase might to some extent be due to harmful effects of maintenance medication and treatment. However, very few of the episodes were related to adverse effects of methadone or buprenorphine. Most probably this increase does not reflect a true increase in non-drug-related morbidity during treatment, but – as discussed above – changes in help-seeking behaviour because of closer follow-up.

Post-treatment period – selection effects in OMT cohort studies

In our study the crude IRR for drug-related episodes between the post- and during-OMT periods was 11.1 (95% CI 6.6 – 18.5) for the whole group, while the interaction analysis showed a ratio among patients with interrupted OMT of 5.4 (95% CI 3.0 – 9.7). This illustrates a general aspect concerning OMT cohort studies: while the pre- and during-treatment periods comprise the whole cohort, the post-OMT incidence rates refer only to those with interruption of treatment. Patients often leave OMT because of problems in treatment like ongoing drug-taking and other forms of risk-taking behaviour. Hence, it is conceivable that the OMT interrupters as a group differ from those with non-interrupted treatment, and that they may have suffered increased risk for drug-related incidents also before and during treatment. In our study only 15% of those who left OMT were assessed as stable and drug-free when leaving treatment, the rest left OMT because of “problems in treatment”. When comparing the interrupter group with those without interruption, we found – perhaps surprisingly – no significant differences concerning the pre-OMT characteristics, including pre-OMT incidence rates for all drug-related treatment episodes. However, the interrupter group scored significantly higher on drug-taking and overdoses during OMT than those without interruption of treatment.

This phenomenon, the overrepresentation of patients experiencing “problems in treatment” as a sign of ongoing risk-taking and upholding of a drug-dominated lifestyle among patients with interrupted OMT, is important in the interpretation of post-treatment outcomes in OMT cohort studies. This is of special importance concerning events related to illicit drug use. In our study – as stated at the beginning of this section – the interaction analysis showed that the increase in the crude incidence rate of drug-related episodes after interruption of OMT compared to the in-treatment period only partially could be explained by this selection effect.

Estimation of mortality rates after OMT interruption in OMT cohort studies may be influenced by similar selection effects. Mortality and morbidity are different phenomena, however, there is intuitively a relation, though complex, between morbidity and mortality and it is likely that changes in morbidity more or less will mirror changes in mortality. For instance, the ratio between fatal and non-fatal heroin overdoses has been estimated to between 1:20 and 1:30⁸⁵. We found a significant increase in drug-related episodes after OMT interruption within the interrupter group and this may indirectly shed light on estimations of mortality after leaving OMT in OMT cohort studies^{89,165,166} and strengthen the assumption that mortality increases after OMT interruption among patients showing high-risk behaviours during OMT.

Sample size

Study 1 was conducted in 2005/2006 with 35 participants from one municipality. 278 disease incidents were registered. There were statistically significant reductions in overall number of disease incidents, in substance-related incidents and in injection-related incidents during OMT as compared to the out-of-OMT period and there was a non-significant tendency towards reduction in non-fatal overdoses.

Considering these results a sample/cohort size of about 200 was estimated as sufficient to evaluate whether non-significant tendencies in Study 1 would prove to be significant in a larger sample. A cohort from a greater geographical area consisting of municipalities of different size and character would also balance possible distinctive qualities concerning the municipality in Study 1 (Gjøvik). Further, this was a study based on patient interviews and in-depth scrutiny of full-text hospital records and thus labour-intensive. With the available resources for the study, it would not have been possible to include considerably more patients.

The sample in Study 2 included only 51 OMT interrupters and the overall post-OMT patient years were limited, especially from post-OMT year two onwards. Thus the number of post-OMT episodes and in consequence the power of statistical analyses concerning this period, was low. This is exemplified by the number of drug-related treatment episodes where the total number of episodes showed a significant reduction during OMT, while when examining each specific type of drug-related episodes, no significant reductions were found although the estimated effects were equally large.

External validity

The study was performed within the Norwegian OMT setting. Specific characteristics of importance among dependent opioid users in Norway are that HIV prevalence is low and that injecting is the dominant route of heroin administration. Further, the study was conducted in an area without major cities, and major cities tend to attract socioeconomic deprived and marginalized dependent opioid users.

Moreover, the cohort is rather old. When OMT was started in Norway as late as in 1998 there was an accumulated group of older dependent opioid users who dominated among patients taken into treatment the first years. Besides, during the first years of OMT in Norway, the age limit for OMT admittance was 25 years (it is now abolished). These factors account for the high mean age of 37 years at OMT entry, and the long mean durability (12 years) of opioid dependence before the first admittance to maintenance treatment. The cohort is representative for Norwegian OMT patients, but the age distribution is no doubt characterised by these specific historical traits of the Norwegian OMT programme, and this might be a potential limitation to the external validity of the study. Age at first OMT admittance did not, however, influence the before-versus-during-OMT reduction in drug-related episodes, but patients with fewer years of opioid dependence before OMT showed less reduction in incidence rates during compared to before treatment.

Brief summary of strengths and limitations

Limitations

1) The studies assessed acute/subacute somatic disease incidents treated by health care services and not morbidity as such. Even so, we assume that changes in treatment episodes are principally in accordance with changes in acute morbidity, as discussed above.

2) In Study 2 (Paper 2 and Paper 3), only hospital contact was examined. In the previous study (Paper 1), GP contacts were registered as well, and between 80 and 85% of all acute somatic disease incidents assessed as severe were found to lead to hospital treatment. Study 2 therefore focused on hospital-treated episodes exclusively and this was considered sufficient to evaluate changes in the most severe disease incidents that are potentially life-threatening or may cause severe or permanent health damage. Thus Study 2 did not assess less severe morbidity not resulting in hospital contact.

3) Both studies focus on acute/subacute morbidity. Problem opioid users, especially those injecting, also experience increased chronic morbidity^{34,167,168} and suffer increased mortality due to various kinds of diseases⁶¹.

4) The list of categories of disease incidents differentiating between drug-related and non-drug-related episodes, and injecting-related and non-injecting-related episodes, was not validated by external researchers. We could find no appropriate list in the literature. There may be uncertainty about these distinctions, e.g. how to determine whether an infection is related to drug-use or recent injecting. However, the inter-rater reliability was good. The fact that we found great reductions in drug- and injecting-related infections during OMT while infections assessed as not related to drug use showed a slight increase, may indicate that the distinction, at least to a considerable extent, was valid.

5) In Study 2 out-of-treatment time was split in time prior to the first admittance to OMT and time out of treatment after the first interruption of OMT (post-OMT time). There were analytical problems due to the fact that the post-OMT period comprised only 91 patient years versus 1000 before and 813 during treatment. This imbalance is due to the very high retention in OMT in Norway and would have persisted even with increased sample size.

6) The number of OMT interrupters was low and in consequence the power of statistical analyses concerning the post-OMT period was low.

7) The external validity may be influenced by specific traits of the Norwegian OMT programme, as discussed above.

Strengths

- 1) High participation rate among patients in as well as out of OMT when invited.
- 2) The Norwegian OMT programme has a catchment area organisation and is part of the public hospital system, parallel to the organisation of the public somatic hospitals. This simplified the collection of data and made it possible to trace almost all hospital contacts.
- 3) In-depth examination of all full-text records made it possible to collect data that were more detailed and robust than interview data (that may lack exactness because of recall bias and patients' interpretations) and register data alone.
- 4) A long observation period comprising both pre-, during and after OMT time.
- 5) Key rehabilitation data on all OMT patients are registered annually within the OMT programme since 2001 and data on drug taking during treatment could be gathered from this register.
- 6) Although data were collected retrospectively (after inclusion), all data on treatment episodes, treatment interruption and drug-taking during OMT were gathered from hospital records and registers and because of this "historic prospective" design, loss to follow-up was no problem.

6 Conclusion

The two studies included in this thesis demonstrate a considerable reduction in acute and subacute somatic disease incidents leading to health service treatment during OMT as compared to the pre-OMT period. This finding holds even for patients taking illicit drugs during OMT. Among OMT interrupters acute and subacute drug-related somatic morbidity is substantially increased after interruption of maintenance treatment, especially the first months. These findings should have implications on how to treat unstable and dysfunctional patients within OMT programs.

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Appendix

Somatisk helse blant opioidavhengige før, under og etter legemiddelassistert rehabilitering (LAR)

Intervjuskjema

Inndeling

- A Opplysninger om intervjuet
- B Demografiske data
- C LAR-historie
- D Spesifikk helse – akutte somatiske sykdomsepisoder
- E Spesifikk helse – kroniske somatiske sykdommer
- F Egen oppfatning av helse- og livskvalitet (5-delte skalaer)
- G Egen oppfatning av forhold til helsevesenet (sykehus, legevakt, fastlege), (5-delte skalaer)
- H Mental helse siste to uker
- I Bruk av rusmidler siste 30 dager
- J Bruk av medikamenter siste 30 dager
- K Intervjuers vurdering av informant og informasjon

Først vil jeg takke deg for at du har sagt deg villig til å delta i denne undersøkelsen. Det er viktig å studere hvordan LAR virker inn på ulike sider av pasientens liv, både for behandlingsapparatet, og ikke minst for pasientene. Dette er en studie av de helsemessige effektene av LAR, og jeg vil stille deg en del spørsmål om helse og sykdommer du har hatt og om dine erfaringer med helsevesenet. Jeg vil igjen understreke at de opplysningene du gir er strengt konfidensielle, og bare vil bli brukt i dette forskningsprosjektet. De vil ikke være tilgjengelige for behandlere i LAR eller andre behandlere.

A Opplysninger om intervjuet

- 1 Løpenummer _____
- 2 Kommunenummer: _____
- 3 Dato fullført intervju: _____
- 4 Type intervju:
 - 1 Personlig på kontor-institusjon _____
 - 2 Personlig hjemme hos pasient _____
 - 3 Personlig annet sted _____
 - 4 Telefon _____
- 5 Hvem har gjennomført intervjuet: _____

B Demografiske data

- 1 Kjønn: 1
 - 1 Mann: _____
 - 2 Kvinne: _____

- 2 Nasjonalitet (statsborgerskap):
- 1 Norsk: _____
 - 2 Vesten: Vest-Europa-USA-Canada- Australia-NZ: _____
 - 3 Øst-Europa: _____
 - 4 Utenfor Europa/Vesten: _____
 - 5 Ukjent: _____
 - 9 Ubesvart _____
- 3 Fødeland pasient:
- 1 Norsk: _____
 - 2 Vesten: Vest-Europa-USA-Canada- Australia-NZ: _____
 - 3 Øst-Europa: _____
 - 4 Utenfor Europa/Vesten: _____
 - 5 Ukjent: _____
 - 9 Ubesvart: _____
- 4 Alder ved intervju (år): _____
- 5 Sivilstatus nå:
- 1 Gift/partnerskap: _____
 - 2 Samboer: _____
 - 3 Skilt/separert, ikke samboer: _____
 - 4 Enslig: _____
 - 5 Annen: _____
 - 6 Ukjent: _____
 - 9 Ubesvart: _____
- 6 Antall egne barn: _____
- 7 Antall barn under 18 år som du har omsorgsansvaret for: _____
- 8 Høyeste gjennomførte utdanning:
- 1 Ikke fullført grunnskole (7-9 år): _____
 - 2 Fullført grunnskole: _____
 - 3 Fullført videregående skole (12 år): _____
 - 4 Høyskole-universitet: _____
 - 5 Ukjent: _____
 - 6 Ubesvart: _____
- 9 Hvor lenge har du vært i vanlig, lønnet arbeid (ikke gjennom sosialkontor, Aetat eller trygdekontor og ikke "svart" arbeid):
- 1 <1år: _____
 - 2 1-5 år: _____
 - 3 > 5år: _____
- 10 Hvor har du bodd de siste 30 dager:
- 1 Hjemme, i min vanlige bolig _____
 - 2 I behandlingsinstitusjon eller sykehus _____
 - 3 I fengsel _____
 - 4 Hos venner/familie _____
 - 5 Annet _____
 - 6 Ukjent _____
 - 9 Ubesvart _____

C LAR-historie (Spørsmål 1-8 besvares ut fra journalopplysninger i LAR-Øst, 9-11 i intervjuet)

- 1 LAR-start mnd/år: _____
- 2 Alder ved LAR-start (år + mnd.): _____
- 3 LAR-slutt mnd/år : _____, evt. flere:
- 4 Evt. re-inntak i LAR, mnd./år: _____, evt. flere:
- 5 Årsak LAR-slutt (første gang, evt ved senere avslutninger):
 - 1 Ekskludert pga. brudd på behandlingsavtale ("aktiv utskrivning"): _____
 - 2 Utskrevet pga ikke hentet LAR-medikament over tid ("passiv utskrivning"): _____
 - 3 Frivillig rusfri: _____
 - 4 Frivillig ikke rusfri: _____
 - 5 Død: _____
 - 6 Annet: _____
- 6 Måneder i LAR: _____
- 7 Måneder mellom LAR-perioder: _____
- 8 Måneder etter LAR: _____
- 9 LAR-medikament ved start:
 - 1 Metadon: _____
 - 2 Subutex: _____
 - 3 Suboxone: _____
- 10 Skifte av LAR-medikament (til hva/når/evt. flere ganger):

- 11 LAR-medikament og dose ved intervju
 - 1 Metadon: _____ dose: _____
 - 2 Subutex: _____
 - 3 Suboxone: _____

D Spesifikk helse – akutte sykdomsepisoder

Formålet med denne studien er å studere helsetilstanden til personer som er eller har vært med i LAR – før, mens og evt. etter at de har vært med i LAR. Vi er først og fremst interessert i mer alvorlige kroppslige sykdomstilfeller som du er blitt behandlet for ved somatiske sykehus, evt. legevakter. Etter intervjuet vil vi gjennomgå journaler fra sykehus og andre steder du har fått behandling.

Jeg vil derfor nå stille noen spørsmål om hvilke sykdommer du har hatt og ved hvilke somatiske sykehus du har fått behandling tidligere i livet, og spesielt de siste 5 år før du startet i LAR, de første 5 år du var i LAR og evt. i tida etter at du sluttet i LAR. (Noter også episoder som kan være lenger tilbake enn 5 år før LAR).

Har du vært innlagt eller fått behandling ved noen av disse sykehusene de siste fem år før LAR eller senere og kan du huske omtrent når, og hva som feilte deg? (Når episoder nevnes, også føre dem inn under avsnittet om episoder registrert etter diagnosegruppe nedenfor, slik at man slipper å spørre/registrere dobbelt).

Gjøvik:

Lillehammer:

Hamar:

Elverum:

Tynset:

Kongsvinger:

Hønefoss:

Har du vært innlagt på eller fått behandling ved sykehus utenfor Oppland og Hedmark?

Oslo:

Andre steder:

Har du fått behandling ved legevakt eller ambulansetjeneste de siste 5 år før LAR eller senere:

Før alle:

Hvilke allmennleger/legesenter har du brukt de siste 5 år før LAR eller senere:

Før alle:

Har du hatt følgende sykdommer/skader?

(Spørre om innleggelser/behandling i sykehus/legevakter som evt. ikke ble husket i forrige del, ikke gjenta episoder som det alt er opplyst om): Kan du si omtrent når du hadde sykdommen? Dersom du fikk behandling for sykdommen, hvor (sykehus/legevakt/legekontor...) fikk du behandling.

For de aktuelle sykdommer spørres: Har du hatt: Ja/nei? Fått behandling (ja/nei) ? Behandling:
Hvor? Når?

Rusrelatert sykdom

- 1 Overdoser/forgiftninger (tilstand der du pga. rusmidler ble bevisstløs eller ikke i stand til å ta vare på deg selv) Antall overdoser med bevisstløshet gjennom hele livet: (Ring rundt rett alternativ).
- 1) 0 2) 1-2 3) 3-10 4) >10
- 1b) Overdoser i LAR-perioden:
- 1) 0 2) 1-5 3) >5

Sykdom relatert til injisering – Jeg vil nå spørre om en del sykdommer som ofte har sammenheng med bruk av sprøyter:

- 2 Blodpropp i armer, bein eller lunger (dyp venetrombose i armer/bein og lungeemboli):
- 3 Akutte virusinfeksjoner som kan smitte ved sprøytodeling
(Akutt Hiv-infeksjon. Akutt hepatitt B- eller Hepatitt C-infeksjon, spør etter ”gulsott”):
- 4 Lokal infeksjoner i hud og underhud, abscess (byll), erysipelas (rosen), flegmone:
- 5 Alvorlige infeksjoner som spres i kroppen (blodforgiftning, infeksjon i hjerteklaffer, beinvev, mellomvirvelskiver, dype og alvorlige bløtvevsinfeksjoner som nekrotiserende fasciitt eller annen alvorlig infeksjon):
- 6 Annen sykdom relatert til injisering:

Annen sykdom relatert til bruk av rusmiddel:

Jeg vil nå spørre om en del andre sykdommer som ofte har sammenheng med rusmiddelbruk:

- 7 Kraftig abstinensreaksjon med eller uten delirium eller kramper:
- 8 Akutt episode relatert til underernæring, utmattelse eller alvorlig nedsatt allmenntilstand som har medført innleggelse/behandling:
- 9 Nyreskade eller nerve-/muskelskader etter langvarig bevisstløshet i forbindelse med rusmiddelbruk (nyresvikt, drophand/dropfoot, forbigående eller varige lammelser/nerve/muskel-skader):
- 10 Annen akutt sykdom med sammenheng til rusmiddelbruk:

Ikke rusrelatert sykdom:

Jeg vil nå spørre om en del andre sykdommer som ofte ikke har sammenheng med bruk av rusmidler:

- 11 Infeksjoner: Luftveier – lungebetennelse, andre betydelige infeksjon (ikke bagateller – forkjølelse mm.), Urinveier: Nyrebekkenbetennelse, andre urinveisiinfeksjoner , Annet.
- 12 Kreft:
- 13 Annen akutt sykdom (hjerte/kar, fordøyelsessystem, nevrologi mm.):

Skader:

Jeg vil nå spørre om skader, jeg tenker da på større skader som har ført til behandling ved sykehus, poliklinikker eller legevakter.

- 14 Hode/ansikt skader (ikke kutt- eller skuddskade):
- 15 Brudd (ikke hode/ansikt):
- 16 Bløtdelsskade (ikke hode/ansikt og ikke kutt/skudd):
- 17 Kuttskade:
- 18 Skuddskade:
- 19 Annen skade:

E Kroniske sykdommer

Jeg vil nå spørre om du har betydelige kroniske sykdommer/helseproblemer, om du er under behandling for dette og om du bruker medisiner for det.

(For hver kategori spørres har/har ikke – hvilken sykdom – behandling/ikke behandling – hvor behandling – og medisiner).

- 1 HIV:
 - 1 Ja: _____
 - 2 Nei: _____
 - 3 Vet ikke: _____
 - 4 Ikke besvart: _____
- 2 Kronisk hepatitt B ("smitteførende"):
 - 1 Ja: _____
 - 2 Nei: _____
 - 3 Vet ikke: _____
 - 4 Ikke besvart: _____

- 3 Hepatitt C:
- 1 Nei, ikke smittet
 - 2 Nei, gjennomført behandling, ikke tilbakefall
 - 3 Ja, gjennomført behandling, men tilbakefall
 - 4 Ja, antistoff positiv, negativ PCR ("ikke påvist virus i blodet"): _____
 - 5 Ja, antistoff positiv, positiv PCR positiv ("påvist virus i blodet"): _____
 - 6 Ja, antistoff positiv, ukjent PCR ("ukjent om virus i blodet"): _____
 - 7 Vet ikke: _____
 - 8 Ikke besvart: _____
- 4 Kreft/ondartet sykdom
- 1 Ja: _____
 - 2 Nei: _____
 - 3 Vet ikke: _____
 - 4 Ikke besvart: _____
- 5 Annen sykdom
- 1 Ja: _____
 - 2 Nei: _____
 - 3 Ikke besvart: _____

F Egen oppfatning av helse- og livskvalitet

Mange har fått et bedre liv i LAR, mens andre har hatt mer problemer. Jeg vil nå stille noen spørsmål om hvordan du mener LAR har virket inn på helsa di og livskvaliteten din. Du skal angi ett svaralternativ på hvert spørsmål.

Ring rundt valgt alternativ:

Før alle:

- 1 Hvordan har den fysiske helsa di vært i LAR-perioden sammenlignet med de siste 5 år før LAR?
- 1 Mye dårligere
 - 2 Litt dårligere
 - 3 Uendret
 - 4 Litt bedre
 - 5 Mye bedre
- 2 Hvordan har den psykiske helsa di vært i LAR-perioden sammenlignet med de siste 5 år før LAR?
- 1 Mye dårligere
 - 2 Litt dårligere
 - 3 Uendret
 - 4 Litt bedre
 - 5 Mye bedre

- 3 Hvordan har livet ditt (livskvaliteten) – i det store og hele - vært i LAR-perioden sammenlignet med de siste 5 år før LAR?

- 1 Mye dårligere
- 2 Litt dårligere
- 3 Uendret
- 4 Litt bedre
- 5 Mye bedre

Bare for dem som svarer litt/mye dårligere livskvalitet i spm. 3:

- 4 Du synes livskvaliteten din er blitt dårligere etter at du startet i LAR. Kan du angi de viktigste årsakene til at livskvaliteten har blitt dårligere? (Spørsmålet stilles åpent, noter inntil to stikkord, spør også spesifikt om den viktigste årsaken, som noteres som nr. 1. Noter formuleringer mest mulig ordrett).

Stikkord:

1, viktigst:

2:

Bare for dem som svarer litt/mye bedre livskvalitet i spm. 3:

- 5 Du synes livskvaliteten din er blitt bedre etter at du startet i LAR. Kan du angi de viktigste årsakene til at livskvaliteten er blitt bedre? (Spørsmålet stilles åpent, noter inntil to stikkord, spør også spesifikt om den viktigste årsaken, som noteres som nr. 1. Noter gjerne formuleringer mest mulig ordrett).

Stikkord/formuleringer:

1, viktigst:

2:

Bare for dem som har avsluttet LAR:

- 6 Hvordan har den fysiske (kroppslige) helse di vært etter LAR-perioden sammenlignet med tida i LAR?

- 1 Mye dårligere
- 2 Litt dårligere
- 3 Uendret
- 4 Litt bedre
- 5 Mye bedre

7 Hvordan har den psykiske helse di vært etter LAR-perioden sammenlignet med tida i LAR?

- 1 Mye dårligere
- 2 Litt dårligere
- 3 Uendret
- 4 Litt bedre
- 5 Mye bedre

8 Hvordan har livet ditt (livskvaliteten) – i det store og hele - vært etter LAR-perioden sammenlignet med tida i LAR?

- 1 Mye dårligere
- 2 Litt dårligere
- 3 Uendret
- 4 Litt bedre
- 5 Mye bedre

G Egen oppfatning av forhold til helsevesenet (sykehus, legevakt, allmennlege)

For mange rusmiddelavhengige er forholdet til helsevesenet vanskelig. Dette fører til at mange rusmiddelavhengige ikke får tilstrekkelig medisinsk behandling. Jeg vil derfor nå stille noen spørsmål om hvordan LAR har virket inn på ditt forhold til helsevesenet. Du skal angi ett svaralternativ for hvert spørsmål.

Ring rundt valgt alternativ:

For alle:

1 Når du sammenligner tida før du startet i LAR – gjerne de siste fem årene – med perioden i LAR, har du da i større eller mindre grad fått hjelp for dine helseplager i tida du har vært med i LAR i forhold til tida før LAR?

- 1 I mye mindre grad
- 2 I litt mindre grad
- 3 Uendret
- 4 I litt større grad
- 5 I mye større grad

For dem som svarer at de har fått mindre hjelp for helseplager i LAR (alt., 1-2) i spm. 1:

2 Hva oppfatter du som den viktigste årsaken til at du har fått mindre hjelp til helseproblemer i LAR? (Spørsmålet stilles åpent, noter inntil to stikkord, og marker så alternativ nedenfor som passer best med stikkordene. Spør også spesifikt om den viktigste årsaken, som noteres som nr. 1. Noter gjerne formuleringer mest mulig ordrett).

Stikkord:

1, viktigst:

2:

For dem som svarer at de har fått mer hjelp for helseplager i LAR (alt. 5-6-7) i spm. 1:

- 3 Hva oppfatter du som den viktigste årsaken til at du har fått mer hjelp til helseproblemer i LAR? (Spørsmålet stilles åpent, noter inntil to stikkord, og marker så alternativ nedenfor som passer best med stikkordene. Spør også spesifikt om den viktigste årsaken, som noteres som nr. 1. Noter gjerne formuleringer mest mulig ordrett).

Stikkord:

1, viktigst:

2:

For alle:

- 4 Hvordan oppfatter du den hjelpen du har fått spesielt fra allmennlegene i tida du har vært med i LAR i forhold til tida før LAR?

- 1 Mye dårligere
- 2 Litt dårligere
- 3 Uendret
- 4 Litt bedre
- 5 Mye bedre

- 5 I den grad du har hatt konflikter med allmennlegene du har brukt, har det vært mer eller mindre konflikt i tida du har vært med i LAR i forhold til tida før LAR?

- 1 Mye mer konflikt
- 2 Litt mer konflikt
- 3 Uendret
- 4 Litt mindre konflikt
- 5 Mye mindre konflikt

Bare for dem som har avsluttet LAR:

- 6 Har du i større eller mindre grad fått hjelp for dine helseplager i tida etter LAR i forhold til tida du var med i LAR?

- 1 I mye mindre grad
- 2 I litt mindre grad
- 3 Uendret
- 4 I litt større grad
- 5 I mye større grad

- 7 Hvordan oppfatter du den hjelpen du har fått fra allmennlegene spesielt i tida etter LAR i forhold til tida du var med i LAR?
- 1 Mye dårligere
 - 2 Litt dårligere
 - 3 Uendret
 - 4 Litt bedre
 - 5 Mye bedre
- 8 I den grad du har hatt konflikter med allmennlegene du har brukt, har det vært mer eller mindre konflikt i tida etter LAR i forhold til tida før LAR?
- 1 Mye mer konflikt
 - 2 Litt mer konflikt
 - 3 Uendret
 - 4 Litt mindre konflikt
 - 5 Mye mindre konflikt

H Mental helse siste to uker

Jeg vil nå stille fem spørsmål om hvordan du har hatt det psykisk den senere tid.

Har du i løpet av de siste to ukene var plaget av noe av det følgende?

		Ikke plaget	Litt plaget	Ganske mye Plaget	Veldig mye plaget
1	Vært stadig redd eller engstelig	___	___	___	___
2	Følt deg anspent eller urolig	___	___	___	___
3	Følt håpløshet med hensyn til framtida	___	___	___	___
4	Følt deg nedfor eller trist	___	___	___	___
5	Bekymret deg for mye om forskjellige ting	___	___	___	___

I Bruk av rusmidler

Jeg vil nå stille noen spørsmål om bruk av rusmidler. Hvor mange av de siste 30 dager har du brukt følgende rusmidler?

		Dager
1	Alkohol, ikke til beruselse	_____
2	Alkohol, til beruselse	_____
3	Nikotin	_____
4	Heroin	_____
5	Andre opiat, smertestillende preparater ikke forskrevet av lege	_____
6	Dempende medisin (benzodiazepiner, andre beroligende, sovemedisin.), ikke forskrevet av lege	_____
7	Kokain	_____
8	Amfetaminer	_____
9	Cannabis	_____
10	Tatt rusmiddel med sprøyte	_____

Jeg vil nå spørre om rusmiddelbruk tidligere i livet. Hvor gammel var du første gang du brukte hvert av disse stoffene (alder i år), og hvor mange år har du til sammen brukt dem (hele tall)? (Det spørres om antall år med enhver bruk, også sporadisk (≥ 1 gang pr. år), og om antall år med avhengighetspreget bruk (daglig eller flere ganger i uka) dersom middelet er tilgjengelig).

	Debut?	Antall år all bruk?	Antall år brukt flere ganger ukentlig til daglig?
11	Alkohol	_____	_____
12	Nikotin	_____	_____
13	Heroin	_____	_____
14	Andre opiat, smertestillende preparater	_____	_____
15	Dempende medisin (benzo, andre beroligende, sovemed.)	_____	_____
16	Kokain	_____	_____
17	Amfetaminer	_____	_____
18	Cannabis	_____	_____
19	Tatt rusmiddel med sprøyte	_____	_____

J Bruk av medikamenter

Hvor mange av de siste 30 dager har du brukt følgende medikamenter forskrevet av lege?

- 1 Rivotril/Xanor/Flunipam – hvilke/dager:

_____	_____
_____	_____

- 2 Andre benzodiazepiner (Vival, Valium, Stesolid, Sobril, Alopam, Mogadon o. a.) – hvilke/dager:

_____	_____
_____	_____

- 3 Benzodiazepinlignende sovemedisiner (Imovane, Stilnoct)
– hvilke/dager:

_____	_____
-------	-------

- 4 Opioidholdige smertestillende eller hostestillende medisin
– hvilke/dager:

_____	_____
-------	-------

- 5 ADHD-medisin (Strattera, Ritalin, Concerta) –
hvilke/dose:

_____	_____
-------	-------

K Intervjuers vurdering av informant og informasjon

Ring rundt valgt alternativ:

- 1 Klinisk ruspåvirket:
1 Nei
2 Lett grad
3 Betydelig grad
4 Ukjent
- 2 Holdning til intervjuer/intervjuet:
1 Positiv/vennlig
2 Negativ/fiendtlig
3 Ukjent

- 3 Virker informasjonen i intervjuet troverdig:
- 1 Ja
 - 2 Nei
 - 3 Usikker

Research article

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Somatic health among heroin addicts before and during opioid maintenance treatment: a retrospective cohort study

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Abstract

Background: The long-term impact of opioid maintenance treatment (OMT) on morbidity and health care utilization among heroin addicts has been insufficiently studied. The objective of this study was to investigate whether health care utilization due to somatic disease decreased during OMT, and if so, whether the reduction included all kinds of diseases and whether a reduction was related to abstinence from drug use.

Methods: Cohort study with retrospective registration of somatic disease incidents (health problems, acute or sub-acute, or acute problems related to chronic disease, resulting in a health care contact). Medical record data were collected from hospitals, Outpatients' Departments, emergency wards and from general practitioners (GPs) and prospective data on substance use during OMT were available from 2001 onwards. The observation period was five years before and up to five years during OMT. The cohort consisted of 35 out of 40 patients who received OMT between April 1999 and January 2005 in a Norwegian district town. Statistical significance concerning changes in number of incidents and inpatient and outpatient days during OMT compared with the pre OMT period was calculated according to Wilcoxon signed rank test. Significance concerning pre/during OMT changes in disease incidents by relation to the type of health service contacts, as well as the impact of ongoing substance use during OMT on the volume of contacts, was calculated according to Pearson chi-square and Fisher's exact tests.

Results: 278 disease incidents were registered. There was a reduction in all incidents by 35% ($p = 0.004$), in substance-related incidents by 62% ($p < 0.001$) and in injection-related incidents by 70% ($p < 0.001$). There was an insignificant reduction in non-fatal overdose incidents by 44% ($p = 0.127$) and an insignificant increase in non-substance-related incidents by 13% ($p = 0.741$). Inpatient and outpatient days were reduced by 76% ($p = 0.003$) and 46% ($p = 0.060$), respectively. The disease incidents were less often drug-related during OMT ($p < 0.001$). Patients experienced a reduction in substance-related disease incidents regardless of ongoing substance use, however there was a trend towards greater reductions in those without ongoing abuse.

Conclusion: Although as few as 35 patients were included, this study demonstrates a significant reduction in health care utilization due to somatic disease incidents during OMT. The reduction was most pronounced for incidents related to substance use and injection. Inpatient and outpatient days were reduced. Most probably these findings reflect somatic health improvement among heroin addicts during OMT.

Background

Opioid addicts, especially injecting heroin users, suffer increased health problems [1-3] and reduced health related quality of life (HRQOL) [4-7] as well as increased mortality, compared to the general population [8-10]. This is particularly related to overdoses [11-14], injuries [9], human immunodeficiency virus (HIV)-infection [9,11], viral hepatitis B (HBV) [15,16] and viral hepatitis C (HCV) [16,17] with end-state liver disease and other infections like endocarditis [9], osteomyelitis [18] and others [19,20]. Several studies and case reports demonstrate vulnerability among injecting drug users (IDUs) to rare infectious diseases like tetanus [21], botulism [22,23] and gas gangrene due to *Clostridium* [21,24-27]. Increased prevalence of various psychiatric diseases among substance users is well documented in population surveys and among persons entering opioid maintenance treatment (OMT) [28-33].

In spite of considerable morbidity, drug users frequently neglect their health problems, and diseases may remain untreated. Several studies describe that patients with extensive drug use cause problems in hospitals [34] and are difficult to treat in ordinary general practice. Yet some studies based on central health registers show increased health care utilization, in particular due to intoxications/overdoses, infections related to illicit drug use and injuries [35].

OMT leads to reduced illegal opioid use and injection [36-39] which probably reduces overdoses and infections. It is also likely that OMT improves nutritional status and general health. Moreover, OMT patients may become more motivated to seek medical help, and OMT may remove or at least reduce tension between patients and health service providers, thus leading to improved health care follow-up. It is therefore reasonable to assume that over time OMT will reduce morbidity and mortality. Reduction in mortality during OMT has been shown in observational studies [11], but in two recent meta-analyses of randomised controlled trials (RCTs) mortality reduction could not be documented [36,38]. However, this might be due to problems applying RCT design in studies on OMT effects versus placebo or no treatment [40]. Some studies have shown improved psychological well-being, reduced frequency of self-reported physical health problems, and improved self-perceived HRQOL during OMT [37,41]. Except for this, documentation of OMT-induced health effects is poor [42]. Consequently observational studies with careful design might increase the understanding of OMT effects on health care utilization and also on morbidity.

With a national OMT program implemented during a short time span and a well documented and severe illicit

drug problem [39], Norway is well suited for such studies. The number of IDUs in Norway is estimated to 8 200 – 12 500 persons out of a population of 4.7 millions in 2005 [43]. The number of OMT patients December 31st 2005 was 3 614 [44]. Although heroin is usually injected [45] the prevalence of HIV among heroin users is as low as 1–2% [46]. The cumulative number of IDUs infected with HIV from the early 1980s until 2006 is 528 [46]. The anti-HCV antibody prevalence among IDUs is 70–80% [47] and approximately 2/3 of these are Polymerase Chain Reaction (PCR) positive [48]. The death rate among drug users has been estimated to about 1–2% per year [45]. The number of registered overdose deaths has been high with a peak of 405 in 2001 falling to 231 in 2004 [45]. Severe psychiatric co-morbidity ("double-diagnosis") is documented in about 1/3 of IDUs [49].

The national OMT program keeps overall surveillance of patients entering and leaving. Entrance depends on specific criteria [39]: patients should be at least 25 years old, have been dependent on opioids for "several" years and have undergone abstinence-oriented treatment. Treatment is ended if patients fail to pick up the medication over time, and may be involuntary terminated if patients show continued illicit drug use, sell the OMT-medication or illegal drugs, act threatening or violent towards treatment personnel or show severe lack of willingness to fulfil the program regulations. Authorized regional centres cooperate with municipal social service and GPs. Only methadone and buprenorphine are accepted as substitution medication and the average dosage level is high: 114 mg and 18 mg respectively in 2005 [44]. Retention in treatment – which means the proportion of patients who stay in the program over time – is high, compared to most other countries [39].

The systematic collection of information on all participants in the OMT-program as well as computer-based record systems in primary health care and hospitals make Norway suitable for detailed studies of OMT related health effects. The objective of this study was to investigate health care utilization due to somatic disease before versus during OMT in a cohort of OMT-patients. The hypothesis was that such health care contact would decrease during OMT, mainly due to reduced health problems related to illicit drug use and injection. Further, we wanted to investigate whether such possible reduction would occur only in patients who stayed abstinent from illicit drug use or also among those with ongoing abuse.

Methods

Our study compares health care utilization due to somatic disease before versus during OMT using a retrospective cohort design.

Study population

The study was carried out in Gjøevik, a district town with 28 000 inhabitants and with considerable drug problems. OMT was started locally in 1999, according to the guidelines of the national program. However, over the years the GPs have come to play a more important role than is typical for OMT in Norway. Further, very few patients, even among those with ongoing substance use, have had their treatment involuntarily terminated, rather they have received increased follow-up by GPs and social workers. Outcome concerning social rehabilitation and continued substance use during OMT has been close to national average [50]. By the end of 2005, all 40 patients who had started OMT were still in treatment, and 36 consented to participate in the study. Data were not collected for one person, rendering 35 participants (87.5%). Key characteristics of the study population are summarized in Table 1.

The observation period was five years prior to and up to five years during OMT; the mean observation period during OMT was 35 months. Three patients temporarily terminated OMT and then restarted. Disease incidents and health care utilization that occurred while the three patients were between OMT periods (in total five years) were counted as pre-OMT.

Data sources

Thirty-two of the participants were interviewed about disease incidents during OMT and the years prior to OMT. One of the authors (IS, physician) performed all interviews, which took place in a primary care centre or in the patient's home. As no validated questionnaire suitable for collecting this information was available, a list of relevant diagnoses (Table 2) was used, as well as Time-line Follow-back procedures, in order to facilitate remembering disease incidents and treatment.

Based upon the information obtained in the interviews, records from hospitals, emergency wards and GPs were collected. For the three persons not interviewed, hospital

records were collected based upon information in their GPs' records. All requested records concerning inpatient treatment, treatment in Outpatients' Departments (in Norway these are hospital units), emergency wards (in Norway these are part of the primary health care and staffed by GPs), and 75 out of 82 records from solo GPs and GP groups (in Norway most GPs work together in groups of 3–5 sharing a joint record system) were received and scrutinized. Data collection was concluded in June 2005. All data on diagnosis and health care utilization presented in the study originate from these records. Admissions and health care visits mentioned by patients which could not be verified from records were not included. Records from hospitals and GPs which had not been specified by the participants were not requested.

Measures

A "disease incident" was defined as a health problem, acute or sub-acute, resulting in a health care contact. Only somatic incidents were counted, psychiatric illness was only considered if it caused a somatic incident, e.g. an injury due to self harm. A disease incident could be an isolated case, for instance an overdose, an infection or an injury, or a new incident due to an underlying chronic disease, for instance an asthma attack. Even if a disease incident lead to more than one health care visit, e.g. follow-up visits for a fracture, it was registered as one incident. Routine hospital or GP check ups for chronic diseases or repeated treatment visits for a chronic disease, e.g. hepatitis C, were not included. Disease incidents documented in several records, e.g. from a hospital and a GP, were only counted once. We also counted number of inpatient treatment days (inpatient days) and treatment days in hospitals' Outpatients' Departments (outpatient days) due to the disease incidents we registered.

The full-text records were scrutinized by one of the authors (IS). ICD-10 [51] diagnoses from hospitals and ICPC [52] diagnoses from GPs were registered. Based on record information the disease incidents were categorized

Table 1: Cohort characteristics

	Male	Female
Gender, n (%)	22 (63)	13 (37)
Age at OMT-start, years, mean (range)	37.3 (29.4 – 50.5)	37.5 (27.3 – 50.3)
OMT medication, methadone, n	19	11
OMT medication, buprenorphine, n	3	2
Methadone dosage mg, median (range)	132.5 (100 – 220)	145 (100 – 170)*
Buprenorphine dosage mg, median (range)	22(16 – 32)	22 (20 – 24)
HCV antibody positive, n (%)	21 (95.5)	13 (100)
Receiving anti HCV treatment during OMT, n	1	0
HIV antibody positive, n	0	0
Died during OMT, n	0	0

*One outlier, 580 mg

Table 2: Before/during OMT changes in disease incidents and inpatient and outpatient days. Number of somatic disease incidents* and inpatient and outpatient days* per 100 patient years before and during opioid maintenance treatment (OMT) in 35 patients.

	Before OMT Incidents/treatment days per 100 patient ears	During OMT Incidents/treatment days per 100 patient years	Reduction %	Increase %	P-value**
Substance-related incidents					
Overdoses (non-fatal)	17.7	9.9	44		0.127
Injection-related incidents, total***	40.6	11.8	70		<0.001
Acute thromboembolic incidents	4.6	0.0			
Acute hepatitis	1.7	0.0			
Acute local infection	32.6	10.9			
Acute/sub-acute general infection	1.7	1.0			
Other substance-related incidents	21.7	8.9	59		0.087
Total	80.0	30.6	62		<0.001
Non-substance-related incidents					
Infections	10.3	8.9	14		0.849
Injuries	20.6	19.7	4		0.832
Other incidents	12.6	20.7		64	0.375
Total	43.5	49.3		13	0.741
All incidents	123.5	79.9	35		0.004
Treatment days					
Inpatient days	257.0	61.0	76		0.003
Outpatient days	59.0	32.0	45		0.060

*Definition of disease incident and treatment days, see text

**Wilcoxon signed rank test

***Overdoses not included, subcategories of incidents in italic

by mean of a diagnosis list developed for this study (Table 2). The list differentiates between drug related incidents and others. Drug related incidents were categorized as overdoses, injection related incidents and "others", like rhabdomyolysis and related neuro-muscular damage related to non-fatal overdoses, severe withdrawal reactions, inpatient treatment because of severe exhaustion, malnutrition and poor general condition due to drug use, severe sub-acute dental health problems and several others. The incidents not related to drug use were divided into infections, injuries and "others", the latter including all incidents not fitting into the specific categories.

Inter-rater agreement on relation to substance use and diagnostic categories was estimated for 22 disease incidents in six patients by two independent investigators (IS and another physician). Agreement regarding relation to substance use was perfect with a kappa value (κ) of 1. When diagnostic groups were considered, κ was 0.82.

Information about ongoing use of illicit drugs and alcohol during OMT, based on urinary testing and clinical assessment, was gathered from the annual reports made

for each OMT patient in Norway since 2001 [39]. For four patients the treatment period was too short or provided insufficient information on substance use; thus rendering such information for 31 patients. The annual report scores overall drug use during the last four weeks on a five-point scale. In our study we simplified this to a dichotomized score for the entire treatment period, differentiating between "problematic" use with severe consequences for psychosocial function versus "abstinence or non-problematic use" without such consequences.

Statistics and ethics

Wilcoxon signed rank test was used to compare changes in rates of episodes before versus during OMT. Pearson chi-square and Fisher's exact test were used to evaluate the changes in the proportion of incidents related to substance use as well as assessment of health improvement versus ongoing use of illegal drugs and alcohol during OMT. Inter-rater agreement was estimated according to Cohen's kappa. All statistical calculations were performed in SPSS 14.0.

The Regional Committee for Research Ethics approved the study.

Results

Table 1 gives a summary of basic demographic and treatment characteristics for the patient sample. The gender distribution is typical for IDUs and mean age at OMT start is 37 years. Treatment is high dosage, dominantly with methadone as agonist. Nearly all patients are HCV-antibody positive, reflecting the dominant injecting drug use pattern.

Altogether, 278 disease incidents were registered during the observation period, 197 before and 81 during OMT.

Table 2 presents findings on health care utilization before and during OMT. The overall reduction in disease incidents was 35% ($p = 0.004$). There was a reduction of 62% in substance-related incidents ($p < 0.001$), a 70% reduction in injection related incidents ($p < 0.001$), and an insignificant reduction of 44 and 59% respectively in overdoses and other substance-related incidents. There was an insignificant increase of 13% in non-substance-related disease incidents, exclusively in the group "other", while infections and injuries showed minor change. Inpatient and outpatient days due to somatic disease incidents were reduced by 76% ($p = 0.003$) and 46% ($p = 0.060$) respectively.

Table 3 shows the pre/during OMT shift in the distribution of disease incidents by relation to substance use. Before OMT 62% of the incidents were related to substance use, compared to 36% during OMT ($p < 0.001$).

Table 4 displays health service contacts made during the 278 disease incidents. Forty per cent of all disease incidents during OMT were documented exclusively by GPs, compared with 25% before OMT ($p = 0.02$). Around 90% of all hospital treatment, before as well as during OMT, took place at the local hospital in Gjøevik.

Table 5 shows changes in disease incidents in nine patients with and 22 patients without problematic substance use during OMT. Regarding injection-related inci-

Table 4: Changes in type of health service contact. Before/during OMT changes in distribution of somatic disease incidents separated by type of health service contact. N = 278

	Number of incidents (%)	
	GP*	Hosp+**
Before OMT	49 (25)	148 (75)
During OMT	32 (40)	49 (60)
P-value	0.015***	

*General practitioner
**Hospital/outpatient clinic/emergency ward
*** Pearson chi-square test

dents, there was no difference between the groups, both showing improvement. The reduction in all substance-related incidents was greater for patients without problematic drug use, but the difference was not statistically significant ($p = 0.06$). The reduction in the total number of incidents was significantly greater for patients without problematic drug use ($p = 0.007$).

Discussion

The primary goal of this study was to investigate how OMT influences health service utilization in heroin addicts. The study demonstrates a significant reduction in health care contacts due to somatic disease incidents during the five first years of OMT compared to the five previous years. This is a significant finding. Even if several studies have shown severe morbidity among heroin addicts, and some have found health improvement during maintenance treatment [37,41], we have not been able to find any study systematically comparing somatic morbidity before OMT with morbidity during treatment, based on record information.

The key question regarding the interpretation of our findings is whether the observed reduction in health care utilization can be seen as an indicator of health improvement during OMT compared to the period before. Firstly, how complete was the registration of admissions and health care visits? The study cohort includes nearly all OMT-patients in a defined area; hence selection bias was not a problem. Recall bias could be a problem, greater the further back we go. The patients' information turned out to be chiefly correct, when controlled against the records, regarding type of disease or injury and where treatment had been received, but more imprecise regarding the point of time. Each patient had on average been treated at two GP centres, and approximately 90% of all hospital treatment had taken place at the local hospital which shows a high degree of stability in the relation between treatment services and the patient group in

Table 3: Distribution of somatic disease incidents before and during OMT by relation to substance use. N = 278.

Relation to substance use*	Before OMT (%)	During OMT (%)	P-value**
Related	123 (62)	29 (36)	<0.001
Not related	74 (38)	52 (64)	
Total	197 (100)	81 (100)	

* Inter-rater agreement $\kappa = 1.00$
** Pearson chi-square test

Table 5: Health care utilization versus ongoing illicit drug use during OMT. Number of patients with reduced, unchanged or increased rates of all, substance-related and injection-related somatic disease incidents respectively, in 22 patients with and 9 patients without problematic* illicit drug use during OMT

Diagnose group	Change in incidents during versus before OMT, number of patients				
Illicit drug use	Reduction	Unchanged	Increase	Total	P value**
All incidents					0.007
Abstinence or non-problematic	18	1***	3	22	
Problematic	3	0	6	9	
All substance-related incidents					0.063
Abstinence or non-problematic	18	3****	1	22	
Problematic	6	0	3	9	
Injection-related incidents					0.503
Abstinence or non-problematic	15	6***	1	22	
Problematic	6	2***	1	9	

* Definition of problematic drug use, see text

**Chi-square Fisher's exact test: number of patients with increased versus reduced/unchanged rates of all, substance-related and injection-related incidents respectively, versus illicit drug use during OMT

*** Patients had zero episodes during both time periods

**** Two of the three patients had zero episodes

Gjoevik. The study thus comprises the majority of health service contacts due to somatic disease incidents during the study period.

Secondly, there will be a gap between the volume of disease in any patient sample, and what results in health service contacts, and this is particularly so in a population of IDUs [34]. Due to the structure of the treatment program, contact between patients and the health services was close during OMT, probably leading to increased help-seeking and better medical follow-up and tending to reduce the proportion of disease incidents not resulting in a health service contact. Thirdly, the patients were five years older during the OMT period, leading to increased somatic morbidity. These factors all tend to increase the volume of registered health care contacts during OMT. Hence, when our study still shows a decline in utilization of health services, this most probably is a proxy for an improvement in somatic health status, and moreover, the OMT-induced improvement is probably more extensive than our findings indicate.

Even six out of nine patients with ongoing problematic substance use during OMT experienced a reduction in drug related disease incidents. The most likely explanation is that they stop or at least reduce injecting drugs. However, due to the increase in non-substance-related disease incidents, the majority of patients with problematic substance-use showed an increase in the total number of incidents during OMT. This could be a consequence of changed help-seeking behaviour and better medical follow-up during OMT. If so, this finding reflects improved

follow-up and not a true rise in morbidity. On the other hand, it is conceivable that patients with ongoing drug abuse during OMT are more exposed to disease than those without. However, because of the small number of patients, and some uncertainty concerning the differentiation between patients with and without ongoing problematic substance abuse, these results and their significance should be interpreted with caution.

OMT is often evaluated primarily by its effect on social rehabilitation and continued substance use. According to our findings, this is not sufficient. Drug related disease incidents were reduced even among patients with ongoing abuse, though to a lesser degree. This might question involuntary termination of OMT in patients who still take illegal drugs.

The study has some weaknesses. The cohort is small and limited to one local community. The research instruments, especially the diagnosis categorisation system, have not been validated by other researchers. In addition, it is not always obvious whether a disease incident is related to substance use or not. However, the high level of inter-rater agreement on whether incidents were substance related or not ($\kappa = 1$) implies that this is possible to differentiate.

In spite of these weaknesses, our study of a small patient cohort showed a significant reduction in health care contacts caused by somatic disease incidents during OMT compared to the five years prior to treatment. These findings ought to be further investigated in an enlarged study.

This could bring information about factors influencing somatic health status changes during OMT, like psychiatric co-morbidity or living in a larger city. The design chosen appears suitable for investigating OMT-related changes in somatic morbidity among heroin addicts in Norway.

Conclusion

Even with as few as 35 patients included, this study demonstrates a significant decrease in health care contacts due to somatic disease incidents during OMT compared to the five years before entering treatment. This reduction was most striking for incidents related to substance use, and drug injection in particular. Inpatient treatment days and treatment days in hospitals' Outpatients' Departments were reduced during OMT. These findings most probably reflect an improvement in somatic health status for drug abusers undergoing OMT compared to the period before entering treatment.

Abbreviations

GP – general practitioner (physician)

HBV – hepatitis B virus

HCV – hepatitis C virus

HIV, human immunodeficiency virus

HRQOL, health related quality of life

IDU, injecting drug user

OMT, opioid maintenance treatment

PCR, Polymerase chain reaction

RCT, randomised controlled trial

SPSS, Statistical Package for the Social Sciences

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

IS had the original idea for the study, participated in the planning, carried out the collection of data, performed the statistical analysis, drafted the manuscript and is the primary author of the paper. HW was project leader, main supervisor and participated in the planning of the study and the writing of the article. MB was supervisor and participated in the planning of the study and the writing of the article. ML was supervisor and participated in the planning of the study, the statistical analysis and the writ-

ing of the article. All authors read and approved the final manuscript.

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Changes in somatic disease incidents during opioid maintenance treatment: results from a Norwegian cohort study

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ABSTRACT

Objectives: To examine the effect of opioid maintenance treatment (OMT) on somatic morbidity in a cohort of OMT patients.

Design: Retrospective cohort study.

Setting: OMT programme in two Norwegian counties.

Participants: 200 OMT patients, participation rate 71.2%.

Main outcome measures: Incidence rates (IR) before, during and after OMT for acute/subacute hospital-treated somatic disease incidents (drug-related, non-drug-related, injuries) and rates for inpatient days and outpatient treatment contacts.

Results: IR for drug-related hospital treatment episodes were 76% lower during compared to before OMT (before versus during incidence rate ratio (IRR) 4.2 (95% CI 2.9 to 6.2), $p < 0.001$) and 11 times higher after compared to during OMT (after versus during IRR 11.1 (6.6 to 18.5), $p < 0.001$). For non-drug-related treatment episodes, IR were 35% higher during than before OMT (before versus during IRR 0.7 (0.6 to 1.0), $p = 0.02$) and 32% higher after compared to during OMT (IRR 1.4 (0.9 to 2.2), $p = 0.15$), while injuries showed little change according to OMT status. Although patients with on-going drug-taking during OMT showed less reduction in drug-related hospital-treated incidents during treatment than patients not using illicit drugs, the quartile with most drug-taking showed a significant reduction (before versus during IRR 3.6 (2.4 to 5.3)). Patients who had experienced cessation of OMT showed a significant reduction in drug-related treatment episodes during OMT (before versus during IRR 1.7 (1.0 to 2.9)), although less than patients without OMT interruptions (before versus during IRR 6.1 (3.6 to 10.6)), and a significant increase after OMT cessation compared with during OMT (IRR 5.4 (3.0 to 9.7)).

Conclusion: Acute/subacute drug-related somatic morbidity is reduced during compared to before OMT. This was also found for patients with on-going drug-taking during OMT. However, acute drug-related health problems show an increase after OMT cessation, and this is a matter of concern. Further studies on somatic morbidity after OMT cessation should be carried out.

ARTICLE SUMMARY

Article focus

- Opioid maintenance treatment (OMT) is the most widely used treatment for opioid dependence, but the effects of OMT on physical health problems have received relatively little attention.
- This study investigates how acute somatic morbidity (drug-related, non-drug-related, injuries) varies according to OMT status (before, during, after OMT) in a cohort of 200 OMT patients.
- The research questions were: Is somatic morbidity reduced during OMT compared to before and after treatment? If so, what types of disease incidents are reduced? How is the effect of OMT status on somatic morbidity influenced by various patient characteristics?

Key messages

- Acute drug-related somatic morbidity (overdoses, injecting-related, other) is substantially reduced during compared to before OMT.
- This was also found for 'problem patients' with on-going drug-taking during OMT, but to a lesser degree than for patients not using illicit drugs.

Strengths and limitations of this study

Strengths

- Participation rate was high, selection bias limited, observation period long and the evaluation of morbidity changes was based on assessment of full-text hospital records.

Limitations

- The study focused on acute health problems treated in hospital, but elective hospital contact due to chronic health problems and primary healthcare contacts were not included.

INTRODUCTION

Dependent opioid users, especially those injecting heroin, have increased somatic^{1–3} and psychological morbidity^{3–6} and reduced health-related quality of life.^{7–8} Injecting drug users are prone to chronic bloodborne viral infections, especially HIV/AIDS^{9–10} and chronic hepatitis B¹¹ and hepatitis C,^{11–12} as

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well as acute and subacute bacterial infections and other complications related to injecting.¹³ Opioid dependence is associated with social marginalisation, criminality and socioeconomic deprivation accompanied by malnutrition, chronic diseases and generally impaired health as well as exposure to overdoses and trauma.¹ Mortality among injecting drug users is much greater than in the general population, with a standardised mortality ratio ranging from 5 to 30 in studies from several countries.^{10–14} The main causes of death (in descending order) are overdose, diseases, trauma and suicide.¹⁰

Maintenance treatment, hereafter called opioid maintenance treatment (OMT), has been the most widely used treatment for opioid dependence for the last number of decades.¹⁵ The specific changes in physical and mental health that occur during OMT have received surprisingly little detailed research attention.¹⁶ Maintenance treatment leads to reduced use of illegal opioids and less injection.^{17–18} It also induces tolerance to opioids,^{19–20} and a corresponding decline in drug-related morbidity including overdoses should be expected. Some studies report improved somatic health during OMT based on interviews,¹⁷ clinical assessment²¹ and reduced consumption of inpatient care due to infections,^{22–23} but relatively few studies have investigated OMT-related somatic health effects and morbidity patterns. In a previous study we found reductions in somatic disease incidents treated in hospital or by general practitioners during OMT compared to 'not in treatment'.²⁴ Drug-related incidents were reduced by about two thirds, but non-drug-related incidents showed a non-significant increase (possibly due to closer contact with health services) and injuries showed no change during treatment. These findings were, however, based upon a small sample of patients from one municipality. In order to evaluate the effects of maintenance treatment, it is necessary to study morbidity prior to, during and after OMT. Such studies are scarce, and very few include long-term follow-up.

The present study investigates how somatic co-morbidity varies according to OMT status (before, during and after OMT) in a group of 200 patients. The main hypothesis to be tested was that somatic morbidity is reduced during OMT. More detailed research questions were: (1) What changes in somatic morbidity are found during OMT compared to before and after treatment, and what types of disease incidents are reduced? and (2) How is the effect of OMT status on somatic morbidity influenced by various patient characteristics?

MATERIALS AND METHODS

Design, sample and setting

Methadone and buprenorphine are used as substitution medications in the national Norwegian OMT programme, which began in 1998. On 13 December 2009, 5383 people were in treatment, and 55.7% were receiving methadone and 44.3% buprenorphine.²⁵

Norway has a population of 4.9 million and the target group for OMT is estimated to be about 10 000.²⁵

The study has a retrospective cohort design. The cohort was established in 2007–8 and consists of those admitted to OMT from 1998 until the end of June 2007 in two counties (Hedmark and Oppland) in Norway (figure 1). The participants were recruited through their treatment contacts. Out of a total of 319 patients who started OMT, 38 had no contact with local health or social services at the time of invitation and were regarded as ineligible for this study. Of the remaining 281, 13 who died after their first OMT entry were included. Among the 268 eligible subjects still alive, 187 consented to participate and 81 did not, and so the cohort consisted of 200 persons. The participation rate was 71.2%, 68.8% among patients in treatment versus 73.7% among those not in treatment when invited.

Measures

A somatic disease incident was defined as any acute or subacute health problem leading to inpatient or outpatient hospital treatment, henceforth called hospital treatment episodes, treatment episodes or just episodes. The numbers of hospital treatment episodes, inpatient days and outpatient hospital contacts were recorded. Incidence rates and rates of inpatient days and outpatient contacts for the periods before, during and after OMT were calculated. Incidence rate ratios before versus during treatment and after versus during treatment were estimated. Only records from somatic departments were examined. Psychiatric disease incidents were only considered if they caused a somatic condition, for example due to self-harm. Hospital contacts for chronic somatic disorders were not included, but acute treatment episodes caused by an underlying chronic disease were assessed. One episode could lead to more than one contact, for instance follow-up of a fracture or an abscess. One episode documented in records from several hospitals was only counted once. Episodes were

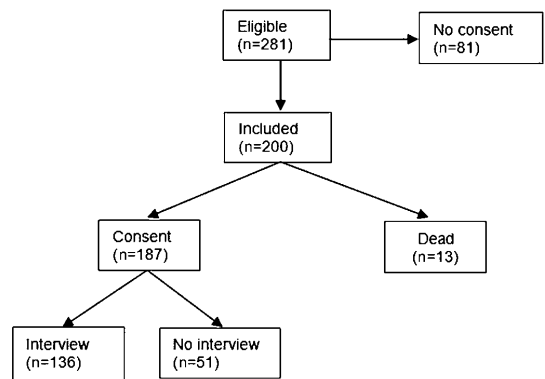


Figure 1 Participants: patients starting opioid maintenance treatment between 1998 and June 2007. The studied cohort consists of the 200 included patients.

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categorised as drug-related (overdoses, injecting-related, other), non-drug-related (infection, other) or injuries.

Data

One hundred and thirty-six of the 187 alive participants (73%) underwent structured interviews which collected information on personal data, former hospital contacts and drug history as well as education and employment history.

Records from somatic departments in local hospitals were examined for all participants. Based on interview information, records from other hospitals were collected and more than 99% of all requested records were examined. Only incidents of somatic disease documented in hospital records were included and records for all 200 participants were examined.

Data were also drawn from annual status reports on each patient in the national OMT programme with information about ongoing drug-taking during OMT based on urine tests and clinical assessment. A combined score based on use of illicit opioids, cannabis, benzodiazepines and central stimulants during OMT was calculated for each patient. Data were obtained for 183 participants (91.5%).

Observation period

Data were studied for the 5 years before first admittance to maintenance treatment, up to the first 5 years during OMT (one or consecutive periods), and up to the first 5 years out of treatment (one or consecutive periods) after first admittance to OMT. Thus, the post-OMT period was defined as the sum of the time between treatment periods and time after the last treatment period. The total observation period was 1000 patient-years before, 813 during and 91 after OMT. The date of collection of their record from the local hospital (during 2008–9) was defined as the study end-point for each patient.

Inter-rater agreement

Inter-rater agreement was established in the pilot study.²⁴ We found high inter-rater reliability for whether hospital treatment episodes were drug-related ($\kappa=1$) and for categories among drug-related treatment episodes (overdose, injecting-related or other, $\kappa=0.82$). In this study, IS (the first author) first scrutinised all full-text records. Treatment episodes considered difficult to categorise were discussed between IS and another physician (the co-author ER) until consensus was reached.

Statistical analyses

Incidence rates were analysed by means of a Poisson regression model. Dependencies in the data, due to the fact that each participant was measured repeatedly (before, during and after OMT), were handled by generalised estimating equations with unstructured working correlation and robust variance estimation. With regard to drug-related treatment episodes, we

investigated the possible influence of different patient characteristics on the effect of OMT by including the interaction between OMT and the characteristic in question in the model, one by one. Incidence rate ratios with 95% CIs were estimated. The significance level was set to 5%. All analyses were performed in SPSS v 15.

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. Exemption from the duty of confidentiality and professional secrecy for those who had died was granted by the Norwegian Directorate of Health.

RESULTS

Cohort characteristics

Sixty-six per cent of the cohort were men and the mean age at the first entry to maintenance treatment was 37 years. Methadone was prescribed to 67% and buprenorphine to 33% at the point of entry to the study. Mean dosage for methadone was 122 mg and 17.6 mg for buprenorphine. Fifty-one out of 200 (26%) had left maintenance treatment once or more during the observation period, while the rest had been in continuous treatment since they were included. Mean age of first use of heroin was 21.1 years, and mean duration of opioid dependence before OMT was 12.3 years. Thirty-four per cent reported more than 10 overdoses during their lifetime, 54% between one and 10, and 12% reported none. Seventeen per cent had not completed 9 years of compulsory schooling, 50% had completed 9 years and 33% had 12 or more years of education. Twenty-three per cent had <1 year of employment, 28% between 1 and 5 years and 49% had more than 5 years of work experience.

Among the patients who had experienced interruption of maintenance treatment, 15% were assessed as stable and drug-free when leaving OMT for the first time, while 85% were assessed as unstable and taking drugs.

Changes in hospital-treated somatic disease incidents

Table 1 shows the rates of hospital treatment episodes due to acute and subacute somatic disease incidents and the rates for inpatient days and outpatient hospital contacts for the various categories of episodes before, during and after OMT. Table 2 displays the statistical significance of these changes by showing the incidence rate ratios according to different OMT status; before versus during OMT and after versus during OMT, respectively. A total of 1021 somatic disease incidents were registered: 605 before, 310 during and 106 after OMT.

The rate of all treatment episodes was 37% lower during compared to the period before treatment (before versus during OMT incidence rate ratio (IRR) 1.6 (95% CI 1.3 to 1.9), $p<0.001$). The rate in the post-OMT period was 197% higher compared to the period during OMT (after versus during treatment IRR 2.8 (95% CI 2.1 to 3.9), $p<0.001$).

During treatment, the rate of all inpatient hospital treatment days was 38% lower (before versus during

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Table 1 Acute/subacute hospital-treated somatic disease incidents: incidence rates and rates of inpatient days and outpatient treatment contacts per 100 patient-years

	OMT status		
	Before	During	After*
Incidence rates			
All acute/subacute incidents	60.5	38.1	113.0
All drug-related incidents	31.9	7.5	75.7
Overdoses	10.4	3.7	20.8
Injecting-related, total**	14.2	2.4	34.0
<i>Deep venous thrombosis/lung embolism</i>	<i>0.6</i>	<i>0.2</i>	<i>1.1</i>
<i>Acute hepatitis B and C</i>	<i>0.9</i>	<i>0.1</i>	<i>1.1</i>
<i>Local bacterial infections</i>	<i>8.5</i>	<i>1.5</i>	<i>19.7</i>
<i>Systemic bacterial infections</i>	<i>3.3</i>	<i>0.5</i>	<i>11.0</i>
<i>Other</i>	<i>0.9</i>	<i>0.1</i>	<i>1.1</i>
Other drug-related, total**	7.3	1.4	20.8
<i>Withdrawal-related</i>	<i>2.7</i>	<i>0.5</i>	<i>4.4</i>
<i>Impaired general condition</i>	<i>1.4</i>	<i>0.2</i>	<i>7.7</i>
<i>Neuromuscular</i>	<i>0.5</i>	<i>0.0</i>	<i>1.1</i>
<i>Other</i>	<i>2.7</i>	<i>0.6</i>	<i>7.7</i>
All non-drug-related incidents	12.4	16.7	21.9
Infections	3.7	4.7	11.0
Other	8.7	12.1	11.0
Injuries	16.2	13.9	15.4
Treatment contact rates			
Inpatient days per 100 patient-years	150.7	92.4	472.8
Drug-related	86.9	13.9	331.3
Non-drug-related	31.7	62.9	69.1
Injuries	32.1	15.6	72.4
Outpatient contacts per 100 patient-years	56.4	41.4	107.5
Drug-related	22.9	4.8	49.4
Non-drug-related	12.1	16.9	26.3
Injuries	21.4	19.8	31.8

The rates before and during OMT refer to all patients, while the rates after OMT refer exclusively to patients with interrupted OMT. Patient-years at risk: 1000 before, 813 during and 91 after OMT. Number of incidents: 605 before, 310 during and 106 after OMT.

*After OMT is defined as time out of treatment (one or more consecutive periods) after first admittance to OMT, that is the sum of the time between treatment periods and time after the last treatment period.

**Subgroups in *italic*.

OMT, opioid maintenance treatment.

treatment IRR 1.7 (95% CI 1.1 to 2.4), $p=0.01$) and the overall rate of outpatient hospital treatment contacts was 27% lower (before versus during treatment IRR 1.4 (95% CI 1.0 to 1.8), $p=0.04$). After treatment the rate of inpatient days was 5.1 times higher than during treatment (IRR 5.9 (95% CI 3.6 to 9.6), $p<0.001$) and the rate of outpatient hospital treatment was 2.6 times higher (IRR 2.0 (95% CI 1.1 to 3.8), $p=0.03$).

Drug-related disease incidents

The rate of drug-related hospital treatment episodes was 76% lower during treatment than before (before versus during IRR 4.2 (95% CI 2.9 to 6.2), $p<0.001$). The rate of injecting-related episodes was 83% lower (IRR 5.9 (95% CI 3.1 to 11.4), $p<0.001$) and the rate of overdoses was 64% lower (IRR 2.8 (95% CI 1.6 to 5.0), $p<0.001$) than before OMT. Among the injecting-related episodes, local and systemic bacterial infections were the most common. The rate of drug-related inpatient days was 84% lower (IRR 6.3 (95% CI 3.4 to 11.8), $p<0.001$) and the rate of outpatient contacts was 79% lower during

treatment compared to the pre-treatment period (IRR 4.8 (95% CI 2.7 to 8.3), $p<0.001$).

The post-OMT rate for drug-related treatment episodes was higher than the rate before or during treatment. Compared to the period during OMT, the rate was 10.1 times higher (IRR 11.1 (95% CI 6.6 to 18.5), $p<0.001$). Overdoses after OMT were double those before OMT and the overdose rate was 5.6 times higher compared to the period during OMT (IRR 5.8 (95% CI 2.7 to 12.3), $p<0.001$). The rate of injecting-related episodes was 14.2 times higher after than during treatment (IRR 12.6 (95% CI 4.3 to 36.8), $p<0.001$), the rate of inpatient days due to drug-related episodes was 23.8 times higher (IRR 25.2 (95% CI 13.1 to 48.7), $p<0.001$) and the rate of outpatient contacts was 10.3 times higher (IRR 10.6 (95% CI 4.7 to 25.9), $p<0.001$).

Non-drug-related disease incidents

Non-drug-related treatment episodes were 35% more frequent during treatment compared to the pre-OMT

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Table 2 Acute/subacute hospital-treated somatic disease incidents: crude incidence rate ratios and treatment contact rate ratios of inpatient days and outpatient hospital contacts

	IRR/TCRR (95% CI)	p Value
Before versus during OMT, during OMT as reference (incidence rate=1)		
All incidents	1.6 (1.3 to 1.9)	<0.001
Drug-related*	4.2 (2.9 to 6.2)	<0.001
Overdoses	2.8 (1.6 to 5.0)	<0.001
Injecting-related	5.9 (3.1 to 11.4)	<0.001
Other	5.7 (2.8 to 11.9)	<0.001
Non-drug-related	0.7 (0.6 to 1.0)	0.02
Injuries	1.2 (0.9 to 1.5)	0.23
Inpatient days		
Drug-related	6.3 (3.4 to 11.8)	<0.001
Non-drug-related	0.5 (0.3 to 1.0)	0.04
Injuries	2.1 (0.7 to 5.7)	0.17
All	1.7 (1.1 to 2.4)	0.01
Outpatient contacts		
Drug-related	4.8 (2.7 to 8.3)	<0.001
Non-drug-related	0.7 (0.4 to 1.2)	0.18
Injuries	1.1 (0.7 to 1.6)	0.78
All	1.4 (1.0 to 1.8)	0.04
After versus during OMT, during OMT as reference (incidence rate=1)		
All incidents	2.8 (2.1 to 3.9)	<0.001
Drug-related	11.1 (6.6 to 18.5)	<0.001
Overdoses	5.8 (2.7 to 12.3)	<0.001
Injecting-related	12.6 (4.3 to 36.8)	<0.001
Other	16.7 (6.5 to 42.7)	<0.001
Non-drug-related	1.4 (0.9 to 2.2)	0.15
Injuries	0.8 (0.3 to 1.8)	0.57
Inpatient days		
Drug-related	25.2 (13.1 to 48.7)	<0.001
Non-drug-related	1.1 (0.5 to 2.3)	0.78
Injuries	4.6 (0.8 to 28.5)	0.98
All	5.9 (3.6 to 9.6)	<0.001
Outpatient contacts		
Drug-related	10.6 (4.7 to 25.9)	<0.001
Non-drug-related	1.6 (0.7 to 3.7)	0.26
Injuries	1.1 (0.4 to 3.1)	0.87
All	2.0 (1.1 to 3.8)	0.03

The incidence rate ratios indicate the statistical significance of the changes in incidence rates demonstrated in [table 1](#), estimated by Poisson regression (generalised estimating equations). Patient-years at risk: 1000 before, 813 during and 91 after OMT. Number of incidents: 605 before, 310 during and 106 after OMT. IRR, incidence rate ratios; OMT, opioid maintenance treatment; TCRR, treatment contact rate ratios.
*Subgroups in *italic*.

period (before versus during IRR 0.7 (95% CI 0.6 to 1.0), $p=0.02$) and both infections and other non-drug-related episodes increased. After treatment there was a 31% increase for all non-drug-related episodes versus the period during OMT (IRR 1.4 (95% CI 0.9 to 2.2), $p=0.15$). The rates for inpatient days and outpatient hospital treatment contacts showed similar changes.

Injuries

The changes in incidence and treatment contact rates for injuries were minor and non-significant.

Interaction between OMT status and patient characteristics

From the data in [table 1](#) it is evident that changes according to OMT status in the total number of hospital treatment episodes are associated with changes in drug-related treatment episodes. In the analysis of how the effect of OMT status is influenced by various patient characteristics, we therefore concentrated on drug-related episodes alone. [Table 3](#) shows the interaction between the effect of maintenance treatment (OMT status) and various patient characteristics, that is the incidence rate ratio between the periods before and during OMT for drug-related treatment episodes adjusted for these characteristics.

In a comparison of patients who received continuous maintenance treatment throughout the during-OMT observation period versus those who left treatment once or more, those with continuous treatment showed greater incidence rate reduction during treatment than those with interrupted treatment, although the latter still showed significant reduction versus the pre-treatment period. After treatment, the group with interrupted treatment showed an increase, with the incidence rate ratio between the periods after and during OMT for this group being 5.4 (3.0 to 9.7) (not shown in the table). Patients with ongoing illicit drug-taking during OMT showed less reduction in incidence rate during treatment than patients not using illicit drugs. Even so, the quartile taking most drugs showed a significant reduction during versus before OMT (before versus during IRR ratio 3.6 (2.4 to 5.3)).

Among the pre-OMT patient characteristics, only employment history and years of opioid dependence before OMT showed a significant interaction with OMT status in the period before versus during OMT. Individuals with less work experience and fewer years of opioid dependence, respectively, showed less reduction in incidence rates during compared to before treatment. Interaction was also tested for gender, age at OMT start, lifetime number of overdoses, years of education and age at heroin debut without showing any statistically significant interaction ($p>0.1$).

DISCUSSION

The study shows a substantial reduction in drug-related hospital-treated incidents of somatic disease during maintenance treatment compared to the pre-treatment period. The reduction consists of less overdoses, and fewer injecting-related and other drug-related treatment episodes.

Overdoses are the most frequent cause of death among dependent opioid users,¹⁰ and the 64% reduction in overdoses during treatment is an important finding. Several studies have documented reduced mortality during OMT compared to the pre-OMT period^{9 26–32} and after leaving OMT,^{33–35} and the reduction in overdoses found in the present study supports previous findings of reduced mortality during OMT.

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Table 3 Acute/subacute drug-related hospital-treated somatic disease incidents: interaction effect between OMT status (before versus during OMT) and patient characteristics

Patient characteristics	p Value for interaction	Adjusted IRR (95% CI)
During-treatment characteristics		
Interruption of OMT	0.001	
Continuous treatment		6.1 (3.6 to 10.6)
Interrupted treatment		1.7 (1.0 to 2.9)
Drug-use during OMT (illicit opioids, cannabis, benzodiazepines, central stimulants)	0.07	
25th Percentile, quartile without drug use		6.5 (3.5 to 12.0)
75th Percentile, quartile with most drug use		3.6 (2.4 to 5.3)
Pre-treatment characteristics		
Employment years	0.02	
<1 year		2.6 (1.3 to 5.2)
1–5 years		4.1 (1.8 to 9.2)
>5 years		5.5 (2.7 to 11.2)
Opioid dependence before OMT, years	0.01	
8 years (25th percentile)		3.3 (2.0 to 5.5)
16 years (75th percentile)		5.4 (3.1 to 9.4)

Adjusted incidence rate ratios (IRR) estimated by Poisson regression (generalised estimating equations) before versus during OMT, during OMT as reference (incidence rate=1). Only characteristics showing significant interaction with OMT status are shown. Crude IRR are shown in table 2. Interaction was also tested for gender, age at OMT start, lifetime number of overdoses, years of education and age at heroin debut without showing significant interaction ($p>0.1$).

Patient-years at risk: 1000 before, 813 during and 91 after OMT. Number of incidents: 605 before, 310 during and 106 after OMT. IRR, incidence rate ratio; OMT, opioid maintenance treatment.

Injecting-related treatment episodes were also substantially reduced (by 83%) during OMT. This may have been due to those OMT patients who stopped injecting and to others who continued to inject but at a less frequent rate than before treatment.²⁸ The reduction includes all kinds of injecting-related episodes among which local and systemic bacterial infections are by far the most frequent. The local skin infections often require surgical treatment and may give rise to severe systemic infections as septicaemia, fasciitis, endocarditis, osteomyelitis, discitis and others. Most of these conditions are rare, but they are much more frequent among injecting drug users than among the general population.³⁶ Such infections may be life-threatening and may result in severe and permanent health problems, and often necessitate complex, long-lasting and expensive hospital treatment. When injecting-related health problems among drug users are considered, these apparently less serious conditions are often overshadowed by the focus on HIV and hepatitis C. However, some studies indicate that the burden on the healthcare system due to injecting-related local and systemic bacterial infections may be even greater than that due to bloodborne infections.³⁷ The present study found that such bacterial infections were frequent among dependent opioid users and that they were substantially reduced during maintenance treatment.

Non-drug-related treatment episodes were found to increase (by 35%) during OMT as compared to the pre-OMT period. Inpatient days increased by 98% and outpatient treatment contacts increased by 40%. The reason for this may be closer contact with health services during maintenance treatment. Within the OMT

programme, patients may receive healthcare that was not previously available to them, leading to the diagnosis and treatment of health problems that were previously not identified.³⁸ If so, this increase in non-drug-related episodes may reflect improved access to health services and not an increase in morbidity. It is theoretically possible that this increase is due to adverse effects of OMT, but we have found no evidence of this in our scrutiny of the hospital records.

Drug-related treatment episodes and related inpatient days and outpatient hospital contacts were more frequent in the period after OMT compared to the periods before OMT and during OMT. These rates apply only to those patients who had left OMT. Although some patients may remain drug-free after leaving OMT, it is likely that many leave OMT, voluntarily or involuntarily, because of ongoing drug-taking, opposition to programme rules and control measures, or instability in taking their OMT medication.^{10 25 31} Our data show that only 15% of those who left OMT were assessed as stable and drug-free at the time of leaving treatment. Patients with interrupted maintenance treatment may therefore constitute a patient subgroup with higher levels of risk-taking behaviour and/or more serious health problems, and the post-OMT results may be influenced by selection bias. We therefore examined the interaction between OMT status (incidence rates before versus during OMT) and OMT cessation (having experienced OMT cessation or not) and found less reduction in drug-related treatment episodes in the cessation group compared to the group with continuous treatment. Nevertheless, even the cessation group experienced a significant reduction in episodes of about 40%. After OMT cessation, however,

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they experienced a more than fivefold increase compared to the period during OMT. The high post-OMT incidence rates, therefore, reflect an increase in acute drug-related health problems after OMT cessation among patients with treatment interruption, and cannot be fully explained by selection effects. This is an important finding that should stimulate increased efforts to study the health effects of OMT cessation and to improve responses to minimise the harmful consequences.

Even the quartile taking most illegal drugs during OMT showed a significant 72% reduction in drug-related treatment episodes during versus before treatment. This indicates that not only patients with successful maintenance treatment, but also patients with poor rehabilitation results experience health improvement during OMT.

The present study focuses on acute/subacute hospital treatment episodes. Injecting drug users experience increased chronic morbidity that reduces their quality of life^{8 39 40} and some studies based on interviews⁴¹ and clinical assessment²¹ show a reduction in chronic health problems during OMT. However, considering the high mortality rate among injecting drug users,¹⁰ the often life-threatening acute disease incidents comprise a substantial—and perhaps the most important—part of the morbidity pattern within this group.

The study has some limitations. First, the study assessed acute/subacute hospital-treated disease incidents and not morbidity as such. A key question is whether changes in incidence and treatment rates according to OMT status (before, during and after OMT) reflect a change in morbidity; in other words, whether these rates can be regarded as a proxy indicator for morbidity. Information on hospital treatment outside the local area was based on patient recall and some disease incidents prior to treatment may have been overlooked. In addition, closer contact with health services during OMT probably increases patients' help-seeking, resulting in hospital treatment for health problems that would not have been treated before OMT. Further, the patients were 5 years older during than before OMT, resulting in an age-dependent increase in morbidity. Even so, we found a significant reduction in treatment episodes during OMT. Therefore, our findings most probably reflect a 'true' reduction in acute/subacute incidents of somatic disease, and hence in acute/subacute somatic morbidity, during compared to before OMT.

Another limitation is that primary healthcare contacts were not included in this study. In our previous study,²⁴ however, general practitioner contacts were registered and we found that about 80% of all acute somatic disease incidents assessed as severe resulted in hospital treatment both before and during OMT. The focus on hospital treatment episodes should therefore provide an adequate assessment of OMT-related changes in severe acute health problems within the cohort. Also, the cohort is relatively old, with a mean age at first OMT

entry of 37 years and mean duration of opioid dependence before the first admission to OMT of 12 years. This reflects the late introduction of OMT to Norway in 1998 with an accumulated demand for maintenance treatment by older patients at programme start and a high recommended age limit for OMT admittance during the first years.⁴² The cohort is typical of Norwegian OMT patients, but the age distribution is no doubt characterised by specific historical traits of the Norwegian OMT programme and this might be a possible limitation to the external validity of the study. However, we did check the effect modification of age at OMT entry (no significant interaction) and duration of opioid dependence before first OMT entry (less reduction among patients with fewer years of dependence) on the rates of drug-related treatment episodes before versus during OMT.

Yet another limitation is that the list of diagnoses to differentiate whether treatment episodes were drug-related or not has not been validated by external researchers and we could find no similar list in the literature. There may be some uncertainty about whether some episodes were drug-related or not; however, inter-rater reliability scores were high. There were also analytical problems due to the fact that the post-OMT observation period was only 91 years versus 1000 before and 813 during OMT. This is mainly due to the high retention in OMT in Norway. The relatively few post-OMT years at risk is a limitation in the study, but with this design and the given retention in treatment, the post treatment period will nevertheless be unbalanced compared to the periods before and during OMT.

The study also has certain strengths. These include the high participation rate among patients in as well as out of maintenance treatment at the time of invitation, the access to all hospital records and the long observation period. The overall participation rate was high (71%) and more than 99% of requested hospital records were obtained. Hence, selection bias was probably of limited importance in the study. Further, the evaluation of morbidity changes is based on in-depth assessment of full-text hospital records which could be expected to give more robust data than interview data or register data alone.

Despite possible limitations in the study design, the findings document a substantial reduction in acute and subacute drug-related disease incidents leading to hospital treatment during OMT compared to the period before OMT. This reduction in somatic morbidity during treatment seems also to be valid for patients with ongoing drug-taking during OMT. However, acute drug-related health problems show an increase after OMT cessation, and this is a matter of concern. Further studies on somatic morbidity after OMT cessation should be carried out.

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Competing interests None.

Ethics approval This study was approved by the Regional Committee for Medical Research Ethics - Southern Norway (REK Sør) and the Norwegian Data Inspectorate.

Contributors IS had the original idea for the study, took part in the planning and developed the questionnaire and the list of diagnoses, carried out interviews, collected record data, performed data analyses and statistical analyses, took part in interpretation of data, drafted and is first author of the article, and is guarantor of the study. MB supervised the study and took part in the planning of the study, interpretation of data and revision of the article. MG contributed to the interpretation of data and took part in revision of the article. ML supervised the study and took part in the planning of the study, interpretation of data and revision of the article. ER took part in the interpretation of record data and revision of the article. MT took part in the interpretation of data, planned and performed the statistical analyses and took part in the revision of the article. HW is project leader and the main supervisor of the study and participated in the planning of the study, interpretation of data and revision of the article.

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Increased somatic morbidity in the first year after leaving opioid maintenance treatment: results from a Norwegian cohort study.

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Abstract

Background/aims: Some patients in opioid maintenance treatment (OMT) leave treatment temporarily or permanently. This study investigates whether patients interrupting their OMT differed from non-interrupters in socio-demographic and drug-use characteristics and investigates acute/sub-acute somatic morbidity among the interrupters, prior to, during, and after OMT.

Methods: Cohort design. Observation period: 5 years prior to, up to first 5 years during, and up to 5 years after interruption of OMT. **Participants:** The sample (n=200) comprised 51 OMT interrupters and 149 non-interrupters. Data on patient characteristics obtained from interviews and OMT register information. Data on somatic morbidity from hospital records.

Measurements: Key patient characteristics among OMT interrupters and non-interrupters. Incidence rates of acute and sub-acute somatic disease incidents leading to hospital treatment (drug-related/non-drug-related/injuries) prior to/during/after OMT.

Results: Interrupters and non-interrupters did not differ in pre-OMT characteristics. Interrupters scored significantly higher on drug-taking and overdose during OMT but had a significant 49 % reduction in drug-related treatment episodes. After interruption of treatment such episodes increased markedly and were 3.6 times more frequent during the first post-OMT year compared to the pre-OMT period ($p<0.001$). This increase was highest during the first months after OMT interruption. 2-5 years after interruption there was no significant increase.

Conclusions: Increased somatic morbidity was found among OMT interrupters during the first year after OMT, and especially during the immediate post-treatment period.

1. Introduction

Opioid maintenance treatment (OMT) has been the most widely used treatment for opioid dependence worldwide during the last decades [1]. Several favourable outcomes for OMT are documented in the literature. Reduced mortality during OMT is shown in studies from different countries [2-8], and reduction in crime and related costs is well established [9-11], as are overall societal economic benefits [9]. Several studies indicate improved health during treatment based on self report [12, 13], clinical assessment [14] and reduced inpatient hospital treatment [15, 16].

The favourable outcomes of OMT are primarily in-treatment effects. Less is known about the situation after interruption of treatment, although increased mortality after OMT interruption has been found in studies from several countries [2, 7, 17-19]. Possible effects of OMT interruption on somatic morbidity are yet poorly studied. Although in some high-threshold programmes a substantial proportion of patients achieve a stable drug-free life after planned OMT cessation [15, 20], interruption of maintenance treatment must primarily be regarded as an indicator of treatment problems arising from patient and/or programme characteristics.

A significant reduction in total drug-related acute and subacute somatic disease leading to hospital treatment for patients who entered OMT was reported in a previous paper from our group [21]. This reduction was also found among those who later interrupted their OMT, though it was less than among those without interruption of treatment. After OMT termination the interrupters had a five-fold increase in drug-related disease episodes compared to the in-treatment period. In the present paper we focus on those who had interruptions of their opioid maintenance treatment and investigate patient characteristics as well as the increase in somatic disease after OMT interruption. The research questions were: Do patients with interrupted OMT differ from other OMT patients in terms of problem behaviours? How does the incidence of somatic health problems within the interrupter group vary before and during OMT and especially throughout the post-OMT period? And, how is the incidence of such problems after OMT interruption influenced by patient characteristics?

2. Material and Methods

2.1 Design, sample and setting

In Norway OMT was started in 1998 as a public nationwide programme organized in parallel with the public hospital catchment area orientation [22]. Thus OMT cohorts from one hospital catchment area may be studied, simplifying investigation of hospital treatment among OMT

patients. The study cohort was established in 2007/2008 and consisted of patients who started OMT from 1998 until end of June 2007 in two counties (Hedmark and Oppland) in Norway. Out of a total of 319 patients who started OMT during this period, 38 could not be reached as they had no contact with local health- and social services and these were regarded as ineligible. Among the 281 eligible, 187 consented to participate, 81 did not. Thirteen who had died after their first OMT admittance were included rendering a study cohort of 200 persons. Fifty-one of these (26 %) had experienced interruption of OMT at least once and these are the focus of this paper. The overall participation rate was 71.2 % (73.7 % among persons not in treatment when invited versus 68.8 % among those in treatment).

Interruption of OMT could be planned or unplanned. Unplanned interruption was defined as any unplanned stop of OMT medication (methadone or buprenorphine) lasting for more than five days [23]. When patients voluntarily or involuntarily were tapering off OMT medication, interruption was defined as the first day without medication.

2.2 Measures and data collection

Out of the 187 included who were alive, 136 (73 %), 35 with interrupted treatment and 101 with continuous treatment, underwent a structured interview which provided information on personal data, former hospital contacts, drug history as well as education and employment history.

Records from somatic departments in the local hospitals were collected for all participants. Based on information from these records and from the interviews, records from other hospitals were gathered and more than 99 % of all requested records were collected. The number of somatic disease incidents resulting in hospital treatment was counted. Somatic disease incidents were defined as any acute or sub-acute somatic health problem leading to inpatient or outpatient hospital contact, below referred to as “hospital treatment episodes”. Elective hospital treatment due to chronic somatic disorders was not included, but acute episodes caused by an underlying chronic disease were registered as new incidents. One treatment episode could lead to more than one contact. An episode documented in records from several hospitals was counted as one episode only. Psychiatric disease incidents were not included unless they caused a somatic condition e.g. due to self harm.

Incidence rates of these treatment episodes were the primary outcome measure and were estimated separately for the periods prior to and during OMT, and for different post-OMT sub-periods. Incidence rate ratios prior to versus during and after versus during

treatment were estimated, as well as post-OMT time sequence comparisons versus the pre-OMT period.

Information about ongoing drug use during OMT and interruption of OMT was gathered from annual reports on each participant from the national OMT programme. These reports separately record the use of illicit opioids, cannabis, benzodiazepines, and central stimulants during the previous four weeks based on urine tests and clinical assessment. A combined score for all four substance classes for the whole OMT period was made for each patient, based on the annual evaluations. Such scores were obtained for 183 participants (91.5 %), 47 (92.2 %) with interrupted treatment and 136 (91.3 %) with continuous treatment.

2.3 Observation period

Hospital record data for each participant were gathered for the five years prior to the first admission to OMT, up to the first five years in treatment (one or consecutive periods), and up to the first five years after interruption of OMT (one or consecutive periods). Time between OMT periods and after the last period was registered as post-OMT. Post-OMT somatic treatment episodes were registered according to the end of the preceding treatment period and divided into different post-OMT sub-periods: month one, months two and three, months four to twelve, and year two to five ("later post-OMT period"). Total pre-OMT observation time was 255 years (mean individual observation time=5 years). Total during-OMT observation time was 193 years (mean individual observation time=3.8 years). Total post-OMT observation time was 91 patient years (mean individual observation time=1.8 years); 50 patient years the first year post OMT and 41 the second to fifth year post OMT. The study end-point for each patient was defined as the date when the record from the local hospital was collected during 2008/2009.

2.4 Categories of disease incidents

Hospital treatment episodes were categorised as drug-related (overdoses, injecting-related, other), non-drug-related or injuries. Among injecting-related episodes were deep venous thrombosis/lung embolism, acute hepatitis B and hepatitis C, local injection site bacterial infections and systemic bacterial infections assessed as related to injecting. Among "other drug-related episodes" were withdrawal-related episodes, incidents related to impaired general condition due to problem drug use and neuromuscular conditions. Inter-rater agreement on whether treatment episodes were drug-related or not ($\kappa=1$) and on sub-categories among drug-related episodes (overdose, injecting-related or other, $\kappa=0.82$) was

established in a pilot study [24]. In the present study, IS (first author) examined all full-text records. Treatment episodes considered problematic to categorise were discussed between IS and ER (co-author) until consensus was reached.

2.5 *Statistics*

Patient characteristics in the groups with and without interruption of OMT were compared by Pearson Chi-Square-test or Fishers exact test for categorical variables and Independent-Samples T-test for continuous variables. Incidence rates for treatment episodes were analyzed using a Poisson regression model. Incidence rates and incidence rate ratios with 95 % confidence intervals were estimated and the significance level was set to 5 %. Dependencies in the data, as each participant was measured repeatedly (before – during – after OMT), were handled by Generalized Estimating Equations with unstructured working correlation and robust variance estimation. Influence of patient characteristics on the health effects of OMT interruption was investigated by including an interaction term between OMT status and the characteristic in question in the model, one by one. Statistical analysis was performed in SPSS ver. 15.

2.6 *Ethics*

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. Exemption from professional secrecy duty of confidentiality for those dead was given by the Norwegian Directorate of Health.

... Table 1 about here...

3. **Results**

3.1 *Sample characteristics*

OMT interrupters (N=51) and non-interrupters (N=149) were compared for gender, age at admission to OMT, age at first heroin use, years of opioid dependence prior to OMT, lifetime number of overdoses as well as for employment and education history. No statistically significant differences were found. Scores for ongoing drug-taking and for overdoses during OMT were significantly higher among those who interrupted their treatment.

Table 1 compares hospital treatment episodes prior to OMT for interrupters and non-interrupters. Except for injuries, which were significantly more frequent among interrupters

and "other drug-related episodes" which were found to be significantly more frequent among non-interrupters, there were no significant differences between the groups.

... Table 2 about here

3.2 *Time sequence analysis of somatic disease episodes*

The total number of drug-related treatment episodes showed a statistically significant reduction during OMT compared to before OMT (Table 2). When regarded separately, overdoses, injecting-related and other drug-related episodes did not show a statistically significant reduction. During the total post-OMT period drug-related episodes were 5.6 times more frequent than during OMT and overdoses, injecting-related and other drug-related episodes all increased significantly when assessed separately. Non-drug-related treatment episodes and injuries did not differ significantly according to OMT status.

Figure 1 shows rates for the various groups of treatment episodes prior to and during treatment and during the post-OMT time sequences for patients with interrupted OMT. Table 3 shows incidence rate ratios between post-OMT year one and post-OMT years two to five respectively, compared to the pre-OMT period. The overall increase in drug-related treatment episodes was greatest during the first months after OMT interruption and overdoses were especially frequent the first four weeks. Among the injecting-related episodes, local skin infections and systemic bacterial infections showed the greatest increase after OMT interruption. Treatment contacts due to "impaired general health condition" also increased substantially. Non-drug-related episodes showed a significant increase during the first post-OMT year compared to the pre-OMT period, while injuries showed stable rates throughout the whole observation period. With regard to post-OMT years two to five ("later post-OMT period"), there was no significant increase in drug-related or non-drug-related episodes compared to the pre-OMT period.

... **Figure 1** about here ...

3.3 *Effect modification*

An interaction of borderline statistical significance ($p=0.06$) within the interrupter group was found between gender and OMT status (first post-OMT year versus pre-OMT period): among men drug-related episodes were five times more frequent post-OMT (IRR 5.0 (2.8 – 8.9)), among women 2.3 times more frequent (IRR 2.3 (1.1 – 4.6)). Age at OMT start, years of

employment, years of education and overdoses during lifetime did not interact significantly. In-treatment characteristics (drug-taking during OMT, overdoses during OMT and having experienced more than one OMT interruption during the observation period) were also tested but did not interact significantly with OMT status. For 41 out of the 51 interrupters data on drug-taking at first OMT interruption were available. Six out of the 41 (15 %) were described as leaving OMT voluntarily and not taking drugs at that time. However, the increase in drug-related treatment episodes the first year after treatment compared to the pre-treatment period was the same among these as among the remaining 35 who left OMT in a non-stabilized phase.

... Table 3 about here ...

4. Discussion

4.1 Main findings

The group with interrupted OMT contact did not differ from the non-interrupters with regard to pre-treatment characteristics, including acute somatic health problems prior to the first OMT admittance. However, interrupters took more drugs and were more exposed to overdoses and experienced less reduction in drug-related health problems during OMT. Only 15 % of the interrupters were rated as drug-free and stable when leaving treatment, the rest left treatment while taking illicit drugs and being in an unstable situation. Interruption of OMT was therefore, for the majority, related to problems in treatment.

The first year after interruption of OMT drug-related morbidity was increased, not only when compared to the in-treatment period, but also to the period prior to OMT. The increase comprised overdoses, injecting-related problems and other drug-related health problems as well as non-drug-related problems. These findings are most likely related to relapse to heroin use as opioid dependent persons are known to be at high risk of relapsing after leaving OMT [25]. The findings support the view that interruption of maintenance treatment is a high-risk situation.

Among the injecting-related treatment episodes injecting site infections and invasive bacterial infections like septicaemia, deep soft-tissue infections and endocarditis were most common after exit from OMT. These conditions can be severe, they may cause permanent health damage and may sometimes be life-threatening and they often result in complicated, expensive and long-lasting hospital treatment [26].

Surprisingly, we found no difference between the patients assessed as drug-free when leaving OMT (15 %) and those taking drugs. However, as the drug-free group is small, only six patients, this result should be interpreted with caution, but it may reflect the difficulties achieving a stable drug-free life after OMT cessation.

4.2 *Limitations and strengths*

One of the limitations of the study is that hospital-treated somatic disease incidents were assessed, and not morbidity as such. However, despite a probable closer contact to health- and social services during maintenance treatment, and an expected increased morbidity due to increasing age, we found a significant reduction in drug-related treatment episodes during OMT among the interrupters. This most probably reflects a substantial reduction in drug-related somatic morbidity. The increase in drug-related treatment episodes found in the first post-OMT year most certainly reflects a major increase in somatic morbidity due to drug taking activities.

Another limitation is that the sample includes only 51 OMT interrupters and that the overall post-OMT patient years are limited, especially from post-OMT year two on. This leads to fewer episodes and lower statistical power, exemplified by the number of drug-related treatment episodes where the total number of episodes showed a significant reduction during OMT, while when examining each specific type of drug-related episodes, no significant reductions were found although the estimated effects were equally large. Further, only hospital contacts were examined, as the study did not assess less severe morbidity not resulting in hospital contact. However, hospital treatment episodes were considered sufficient to evaluate changes in severe and potentially life-threatening acute morbidity. Finally, the list of disease categories differentiating between drug-related and non-drug-related episodes, and between injecting-related and non-injecting-related incidents was not validated by external researchers.

Among the strengths of the study are the long pre-, during- and post-OMT observation periods that made it possible to study long-term health effects of being in OMT and of leaving treatment. The high participation rate makes it probable that the study sample is representative for the OMT interrupters in this region. Also, participants were recruited from a particular catchment area enabling a comprehensive cohort with defined health service connections. This made it possible to trace almost all hospital contacts. And, as evaluation of morbidity changes is based on in-depth examination of full-text records, and almost all requested

records were obtained, the data should be more robust, specific and reliable than interview and register data alone.

4.3 Treatment implications

Our findings have implications regarding the handling of “problem patients” in OMT programmes. Often, OMT interruption will coincide with a crisis in treatment and any problems at that time may continue or deteriorate after leaving treatment. This should draw attention to the need for proactive follow-up when treatment crises emerge, in order to prevent OMT interruption [27]. Patients should not be subject to involuntary discharge from OMT unless continued treatment is considered to increase their mortality and morbidity risks. In general, treatment services should seek to retain “problem patients” in treatment [12]. Re-admittance to OMT should be prompt when patients are ready for it.

5. Conclusion

The study shows a significant reduction in drug-related somatic disease incidents during OMT compared to the five years before entering OMT in patients who later interrupted their maintenance treatment. Interrupters and non-interrupters did not differ in pre-treatment characteristics, but interrupters took more illegal drugs and had more overdoses during OMT. For the great majority interruption of OMT was closely related to problems in treatment, especially ongoing illicit drug-taking. Nevertheless there was a substantial increase in drug-related somatic health problems during the first year after OMT interruption, compared both to the pre- and during-OMT periods. The increase was greatest the first months after leaving OMT, and especially the first month. This suggests relapse to extensive drug use and risk-taking behaviour. Hence, it should generally be a goal to keep “problem patients” in treatment. Patients interrupting OMT should receive special follow-up.

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Table 1. Somatic disease incidents treated in hospital: incidence rates per 100 patient years (95 % confidence interval) the five years prior to the first admission to OMT among patients with and without interruption of OMT.

	Interrupted OMT (N=51)	Continuous OMT (N=149)	P-value
All drug-related	27.5 (21.7 – 34.7)	33.4 (29.5 – 37.8)	0.15
<i>Overdoses</i>	<i>11.0 (7.6 – 15.9)</i>	<i>10.2 (8.1 – 12.8)</i>	<i>0.74</i>
<i>Injecting-related</i>	<i>12.2 (8.6 – 17.3)</i>	<i>14.9 (12.4 – 17.9)</i>	<i>0.32</i>
<i>Other</i>	<i>4.3 (2.4 – 7.8)</i>	<i>8.3 (6.5 – 10.7)</i>	<i>0.05*</i>
All non-drug-related	12.5 (8.9 – 17.7)	12.3 (10.1 – 15.1)	0.94
Injuries	21.2 (16.2 – 27.7)	14.5 (12.0 – 17.5)	0.02*
All incidents	61.2 (52.3 – 71.6)	60.3 (54.9 – 66.1)	0.99

* Statistically significant difference between the groups with interrupted versus continuous OMT, Poisson regression.

Note: Years at risk before OMT: 1000 years (255 in OMT interrupters). Number of incidents before OMT: 605 (156 in OMT interrupters). Among injecting-related disease incidents were reckoned deep venous thrombosis/lung embolism, acute hepatitis B and hepatitis C as well as local and systemic infections assessed as related to injecting.

Table 2. Hospital-treated somatic disease incidents in patients with interrupted opioid maintenance treatment (N=51): crude incidence rate ratios (IRR) according to OMT status (before, during, and after treatment).

Before versus during OMT: during treatment as reference (incidence rate=1)

	IRR	CI 95 %	p-value
All drug-related	1.7	1.0 - 2.9	0.04
<i>Overdoses</i>	<i>2.4</i>	<i>0.9 - 6.1</i>	<i>0.08</i>
<i>Injecting-related</i>	<i>1.5</i>	<i>0.8 - 2.7</i>	<i>0.18</i>
<i>Other</i>	<i>2.0</i>	<i>0.5 - 7.5</i>	<i>0.33</i>
Non-drug-related	0.8	0.5 - 1.5	0.54
Injuries	1.1	0.7 - 1.6	0.80
All incidents	1.3	0.9 - 1.8	0.16

After OMT versus during OMT: during treatment as reference (incidence rate =1)

All drug-related	5.6	3.0 – 9.8	<0.001
<i>Overdoses</i>	<i>4.7</i>	<i>1.7 – 12.6</i>	<i>0.003</i>
<i>Injection-related</i>	<i>4.7</i>	<i>1.9 – 11.2</i>	<i>0.001</i>
<i>Other</i>	<i>10.3</i>	<i>2.7 – 39.0</i>	<i>0.001</i>
Non-drug-related	1.6	0.8 – 2.8	0.12
Injuries	0.8	0.4 – 1.4	0.41
All incidents	2.5	1.7 – 3.5	<0.001

Note: Years at risk: Before OMT 255 years, during OMT 193 years, after OMT 91. Number of incidents: Before OMT 156, during OMT 94, after OMT 104. Poisson regression model (Generalized Estimating Equations).

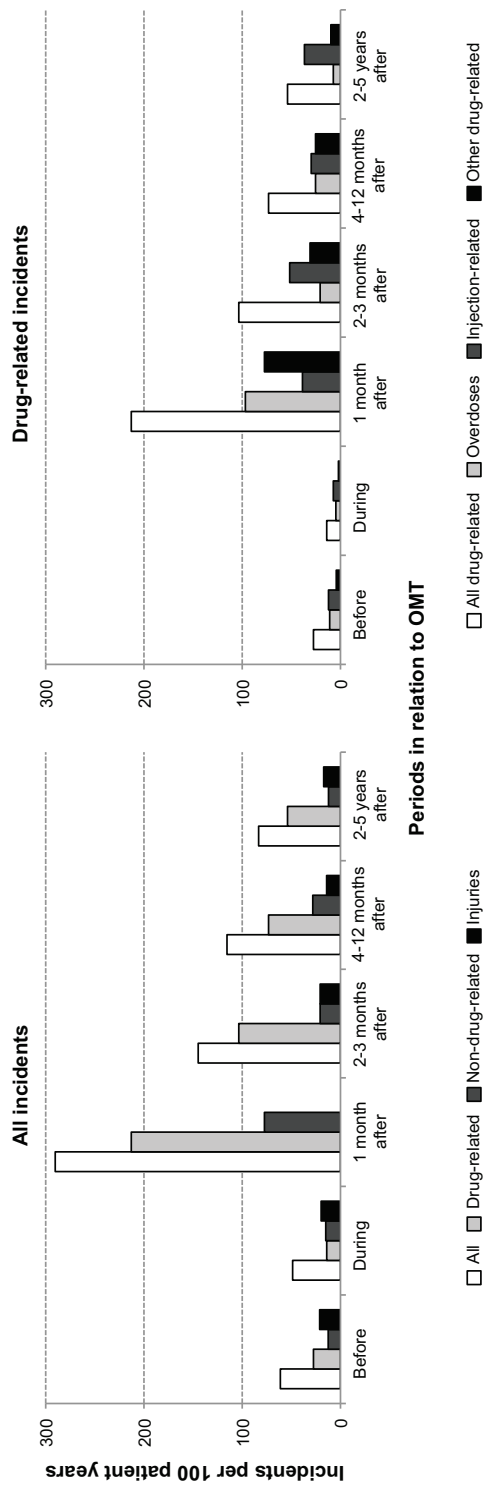
Table 3. Hospital-treated somatic disease incidents among patients with interrupted OMT (N=51): crude incidence rate ratios (IRR) between post-OMT year 1 and post-OMT years 2-5 respectively compared to the five last years before the first admittance to OMT.

Post-OMT year 1 versus pre-OMT period			
	IRR	CI 95 %	p-value
All drug-related	3.6	2.3 - 5.6	<0.001
<i>Overdoses</i>	2.9	1.4 - 6.4	0.006
<i>Injecting-related</i>	2.6	1.3 - 4.9	0.005
<i>Other</i>	7.7	3.4- 17.4	<0.001
Non-drug-related	2.6	1.4 - 4.6	<0.001
Injuries	0.6	0.3 - 1.3	0.23
All incidents	2.3	1.7 - 3.2	<0.001

Post-OMT years 2-5 versus pre-OMT period			
	IRR	CI 95 %	p-value
All drug-related	2.0	0.9 – 4.5	0.11
<i>Overdoses</i>	0.7	0.2 – 2.2	0.49
<i>Injecting-related</i>	2.9	0.9 – 9.4	0.09
<i>Other</i>	2.3	0.9 – 6.0	0.08
Non-drug-related	1.0	0.4 – 2.3	0.93
Injuries	0.8	0.4 – 1.9	0.66
All incidents	1.4	0.8 – 2.4	0.22

Note: IRR estimated by Poisson regression. Patient years at risk: 255 before OMT, 50 the first year post OMT, 41 the second to fifth year post OMT. Number of incidents: 156 before OMT, 70 the first year post OMT, 34 the second to the fifth years post OMT.

Figure 1



Hospital-treated somatic disease incidents in 51 patients with interrupted OMT. Rates for all, drug-related and non-drug-related incidents and injuries (left) and all drug-related incidents and the subgroups overdoses, injecting-related and other drug-related incidents (right) during the last five years before the first admission to OMT, the first five years during OMT (one or consecutive periods) and the first five years after OMT interruption (one or consecutive periods).